body plethysmography and pulmonary capillary blood flow

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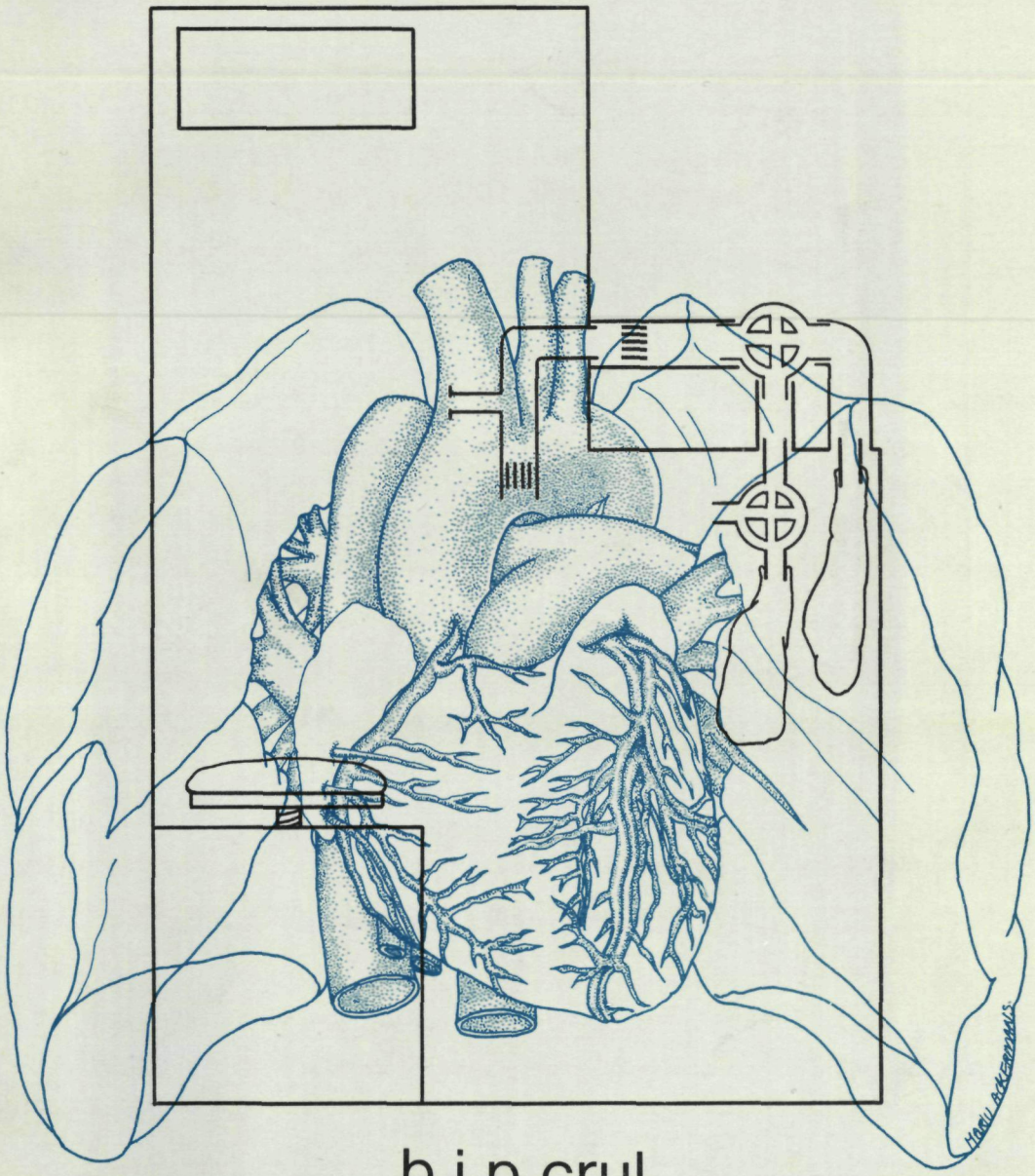
quantitative determination of pulmonary capillary blood flow with the aid of a constant-volume body plethysmograph



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Quantitative determination of pulmonary capillary blood flow with the aid of a constant-volume body plethysmograph

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BODY PLETHYSMOGRAPHY AND PULMONARY CAPILLARY BLOOD FLOW

Quantitative determination of pulmonary capillary blood flow with the aid of a constant-volume body plethysmograph

PROEFSCHRIFT

ter verkrijging van de graad van doctor in de Geneeskunde aan de Katholieke Universiteit te Nijmegen, op gezag van de Rector Magnificus Prof. Dr. A.J.H. Vendrik, volgens besluit van het College van Decanen in het openbaar te verdedigen op 25 juni 1976 des namiddags te 2.00 uur precies,

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Dit proefschrift werd bewerkt in het longfunctielaboratorium (hoofd : Dr. H.H. Beneken Kolmer) van het Instituut voor Anesthesiologie (hoofd : Prof.Dr. J.F. Crul) van het Sint Radboud Ziekenhuis te Nijmegen.

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C O N T E N T S

1.1. Historical notes

In 1910 BORNSTEIN introduced the principle of measuring the amount of blood which flows through the lungs per unit of time. We now refer to this as determination of the 'pulmonary capillary blood flow' (PCB). BORNSTEIN formulated a simple equation to indicate the relation between PCB ($\dot{Q}$) on the one hand and on the other hand the amount of nitrogen absorbed ($\dot{V}_{N_2}$), the alveolar nitrogen fraction ($F_{A_{N_2}}$) and the OSTWALD solubility coefficient of nitrogen in blood (S_{N_2}). The equation is :

$$\dot{Q} = \frac{\dot{V}_{N_2}}{S_{N_2} \times F_{A_{N_2}}}$$

The determination was made after the nitrogen had been washed out of the lungs with oxygen and the subject had resumed breathing air. Due to the low solubility of nitrogen in blood ($S_{N_2} = 0.014$) the amount of this gas taken up by the blood was small; the accuracy of these determinations was consequently poor.

KROGH & LINDHARD (1912) attempted to improve this problematic quantification by using nitrous oxide (N_2O), which is much more readily soluble in blood ($S_{N_2O} = 0.47$). The amount of N_2O taken up by the blood far exceeds the amount of nitrogen taken up by the blood under the same conditions and the accuracy of determination is therefore much higher. Their procedure was as follows. After exhaling deeply the subject inhaled as deeply as possible from a spirometer developed by KROGH, filled with a gas mixture of known composition which contained 10 - 25 % N_2O. The subject held his breath for 5 - 15 seconds (s) and then exhaled at least one litre, whereupon a gas sample was taken. After breath-holding for another 6 - 25 s the exhalation was continued. At the end of it a second gas sample was taken. The samples were both analysed for N_2O, O_2 and CO_2. PCB was calculated from these data, e.g.

with the aid of the BORNSTEIN equation.
However, this method had the following disadvantages :

1) the procedure took 25 - 40 s, within which time recirculation of N_2O occurred;
2) the accuracy of measuring the N_2O concentration had to be very high;
3) the times at which gas samples were taken had to be known exactly, because accurate calculation of the N_2O uptake in the blood depended on it.

GROLLMAN (1929) modified this method by using an inert gas to determine PCB. He used acetylene (C_2H_2), which has the advantage of a higher solubility in blood than N_2O ($S_{C_2H_2} = 0.74$). Moreover, chemical determination of the acetylene concentration was much simpler than determination of the N_2O concentration by physical methods. Objections to GROLLMAN's method focused on the fact that recirculation occurred during the measuring period of 30 - 50 s.

Another modification was introduced by CANDER & FORSTER (1959), who used a mass spectrometer to determine PCB. The N_2O uptake was calculated from the difference in concentration changes between helium (S_{He} = 0.0098) and N_2O during breath-holding at a known lung volume.
The same principle was adopted by AYOTTE et al. (1970), but they used the concentration changes of Freon and N_2O. The gas analysis was done with a gas chromatograph.

1.2.1. Quantitative determination of PCB in the body plethysmograph

In 1955 LEE & DUBOIS were the first to use the body plethysmograph for determination of PCB. Using a manometer they registered the decrease in pressure which occurred in the body plethysmograph when a subject changed from breathing air to breathing a gas mixture containing N_2O. This decrease in pressure results from the uptake of N_2O in the blood flowing through the lungs. After additional determination of the alveolar N_2O fraction, the BORNSTEIN equation can be used to calculate PCB. Determination of PCB by this method is 'instantaneous'.
The uptake of N_2O in the blood flowing through the lungs is followed instantly by a decrease in pressure in the body plethysmograph. In

this way the stroke volume of each heartbeat can be determined. The earlier techniques (e.g. determination of PCB with the aid of an inert gas according to KROGH and according to GROLLMAN) presumed a steady state throughout the determination. The same applies to determination of the cardiac output by the direct Fick method (COURNAND, 1945). These methods differ from determinations of PCB in the body plethysmograph in that the value found for PCB or cardiac output is always a mean value.

LEE & DUBOIS (1955) used the following procedure. A subject was seated in a constant-volume plethysmograph and measuring was started after an adaptation period of a few minutes. The subject was asked to exhale deeply and then to inhale to maximum depth. He then exhaled to resting lung volume and held his breath with open glottis during 5 - 10 s. During this breath-holding the pressure curve of the body plethysmograph was registered. Then followed normal breathing for a few minutes, whereupon the subject again exhaled deeply and inhaled to maximum depth from a balloon filled with oxygen.
This was followed immediately by a deep exhalation and an inhalation to maximum depth from a balloon filled with N_2O. The subject then exhaled to resting lung volume through a Haldane gas sampling tube, again held his breath with open glottis, and registration of the pressure curve in the body plethysmograph was repeated. Finally the subject exhaled to maximum depth through a Haldane gas sampling tube. The gas samples were analysed with the aid of a mass spectrometer.

This determination of PCB, therefore, was based on the execution of two identical breathing manoeuvres : one with air and one with a gas mixture containing N_2O. After suitable calibration, the N_2O uptake could be calculated from the difference in the course of the pressure curves obtained. Calibration was effected by registration of the change in pressure which occurred during pumping of 30 ml air into and out of the body plethysmograph. To calculate the mean alveolar N_2O fraction, an equal distribution of the ventilation-perfusion ratio over the lungs was assumed.
The mean of the two gas samples analysed by the mass spectrometer was taken to be the alveolar N_2O fraction during breath-holding.

When the pressure curve obtained during the air-breathing manoeuvre subtracted from that obtained during N_2O breathing, it was found to show a stepwise declining course synchronous with the heart beat. The N_2O uptake, therefore, was not constant but varied within the duration of a cardiac cycle. LEE & DUBOIS concluded from this fact that the pulmonary capillary blood flow had a pulsatile character. The extent of the pressure change was determined in two ways, firstly by graphic differentiation of the pressure curve and secondly by electronic differentiation of the output signal of the manometer during breath-holding with N_2O. This showed that the pressure change is smallest about 0.1 s after the R- peak of the ECG. A marked change in pressure then follows. Its maximum coincides with the T-wave of the ECG and amounts to about twice the mean pressure change during a cardiac cycle. Next, the pressure change gradually diminishes to half the mean pressure change. These pressure changes were found to be reproducible in consecutive cardiac cycles. During exercise the amplitudes of the pressure changes increased. Since N_2O has a high rate of diffusion, PCB as measured by the N_2O body plethysmograph method represents the blood flow on the arteriolar end of the capillary system. LEE & DUBOIS concluded that PCB has a pulsatile character.

In an effort to establish the influence of respiration on PCB, DUBOIS & MARSHALL (1957) determined PCB during rebreathing in the following way. Two balloons were suspended in the body plethysmograph, one containing air and the other containing a mixture of N_2O and O_2 (ratio 80 : 20). In order to avoid pressure differences due to differences in temperature and water vapour pressure between inspiratory and expiratory air, the air and the $N_2O + O_2$ mixture in the balloons were adjusted to BTPS conditions. The inspiratory and the expiratory pneumotachograms were registered in an effort to estimate the influence of respiration on the pressure changes within the body plethysmograph. Two minutes after being seated in the body plethysmograph, the subject inhaled deeply from the balloon filled with air, and then rebreathed at normal rate and depth for a period of 20 s. The pressure in the body plethysmograph was meanwhile registered continuously. The procedure was repeated after an interval of 2 minutes (min), but this time the subject rebreathed the $N_2O + O_2$ mixture. PCB was calculated from the difference between the two pressure curves obtained and the alveolar N_2O fraction. PCB was found to be little in-

fluenced by normal inspiration or expiration. A slight difference in PCB was established, however, between deep inspiration and deep expiration, PCB being smallest during deep expiration and largest during deep inspiration. VERMEIRE & BUTLER (1968) confirmed this finding.

LINDERHOLM & DUBOIS (1962) compared the determination of PCB with the direct Fick method. For this purpose they designed a constant-volume pressure-sensitive as well as horizontal body plethysmograph, which enabled them to examine subjects in a supine position. After catheterization of the subject they calculated the cardiac output by the direct Fick method. Next, the hood of the body plethysmograph was placed over the subject and closed. The procedure for determination of PCB was the same as that followed by LEE & DUBOIS (1955).

In calculating PCB, correction factors were applied which had not been used previously. Apart from the introduction of a correction factor for leakage from the body plethysmograph to the environment a correction factor was applied for the fact that conditions within the body plethysmograph were not adiabatic. The comparison with the direct Fick method led to the conclusion that the N_2O plethysmograph method yielded fair values for the cardiac output. At a low cardiac output, the method indicated a higher value than that obtained by registration according to the direct Fick method; at a high cardiac output, on the other hand, a lower value was obtained.

BOSMAN, HONOUR, LEE, MARSHALL & STOTT (1964) developed a new technique for registration of N_2O uptake in the body plethysmograph. They equipped the apparatus with a servo-mechanism developed by STOTT (1963). The pressure in the body plethysmograph was kept constant by the insufflation or venting of air. The flow of the air insufflated or vented was continuously registered with pneumotachographs. A volume was obtained by integration of these signals. This measuring method was developed because the body plethysmograph used by LEE & DUBOIS 'tended to be unstable and to drift'. PCB was determined during slow expiration, because breath-holding with open glottis is difficult for many subjects and patients.
The procedure was as follows : the subject exhaled to maximum depth and then inhaled to maximum depth. He then exhaled 'in a

slow and relaxed manner' during 15 s. In this way he first breathed air from the body plethysmograph and immediately afterwards from a balloon filled with a mixture of 80% N_2O and 20% O_2. During the slow exhalation the pneumotachogram of the air insufflated by the servo-mechanism was registered.

These authors, too, obtained a higher value by the N_2O plethysmograph method than by the direct Fick method at a low cardiac output. At a cardiac output of 2.0 l/min the difference between the two methods was 7.5%. At 4 l/min the two methods yielded equal values. At 10 l/min the result obtained by the N_2O plethysmograph method was found to be 5% lower than obtained by the direct Fick method and at 20 min/l it was 10% lower.

BOSMAN et al. found it difficult to decide which method was more accurate. At a high cardiac output, other factors being equal, recirculation of N_2O occurs more quickly. This might explain the lower values obtained by the N_2O body plethysmograph method. Using the direct Fick method, however, even minor disturbances in the steady state can give rise to erroneous results at a high cardiac output.

The correlation which BOSMAN et al. found between their method and the direct Fick method exceeded the correlation which LINDERHOLM et al. found between the two methods: $r = 0.981$, $p = 0.001$ and $r = 0.814$, $p = 0.05$ respectively.
The regression equation Fick method/N_2O plethysmograph method was $\gamma = 0.0902x + 0.45$ according to BOSMAN et al., and $\gamma = 0.43x + 2.80$ according to LINDERHOLM et al. JUCHUMS and WERTZ (1969) compared the values for PCB obtained by the N_2O body plethysmograph method with the values of cardiac output obtained by the dye-dilution method. They found a correlation factor of $r = 0.91$.

1.2.2. Qualitative determination of PCB in the body plethysmograph

Apart from the quantitative features, the qualitative features of the PCB also received further attention. LEE & DUBOIS had already noted that

the flow pattern of the N_2O uptake showed a fixed time relation with the ECG tracings. BOSMAN et al. established that the flow pattern took a different course in patients with heart valve lesions.

KARATZAS & LEE (1969) distinguished the following features in the flow curve of N_2O uptake :

1. The flow pulse conduction time, or briefly 'conduction time'. This is the time lapse between the opening of the pulmonary valve and the start of the ascending leg of the flow curve obtained during slow exhalation of N_2O. The opening of the pulmonary valve is deduced from a simultaneously registered high-frequency phonocardiogram of from the direct registration of the pressure in the pulmonary artery. Under normal conditions the conduction time is 120 milliseconds (ms);
2. The mean acceleration of the blood flow in the capillaries. This is calculated by dividing the difference in flow between the start and the peak of the curve by the time interval between these two points (upstroke time);
3. The amount of blood stored in the pulmonary capillaries during systole. This is calculated by subtracting the integrated blood flow during diastole from the integrated blood flow during the whole cardiac cycle (systolic storage volume);
4. The ratio between maximum capillary flow ($\dot{Q}_c$ max) and mean capillary flow during a cardiac cycle ($\bar{Q}_c$). This is referred to as pulsatility index ($\dot{Q}_c$max $/\bar{Q}_c$).

A supplement to this study was provided by REUBEN (1971). Making use of the findings on pulmonary vascular impedance obtained by ENGELBERG & DUBOIS (1959), SHAW (1963), and by REUBEN, GERSH, SWALDING and LEE (1970), REUBEN was able to determine the mean pressure in the pulmonary artery from the registration of the flow pattern of the N_2O uptake and the phonocardiogram. He was also able to estimate the pressure in the left atrium.

1.2.3. Limitations of determining PCB by the N_2O body plethysmograph method.

The above discussed studies had revealed a number of disadvantages which

concerned recirculation, the distribution of ventilation-perfusion ratios and the breathing procedure. These will be discussed in the following three subsections.

1.2.3.1. Recirculation of N_2O

The amount of N_2O taken up by the blood flowing through the lungs is dependent on the difference between the alveolar N_2O pressure and the N_2O pressure which prevails in the pulmonary artery. It is therefore important to establish whether (and to what extent) recirculation of N_2O occurs. The time required for an inhaled gas to return to the lung via the circulation is known as pulmonary recirculation time (RIGATTO et al. 1968). In subjects lying supine, LAGERLÖF et al. (1948), WERKÖ et al. (1949), CHAPMAN et al. (1950) and RIGATTO et al. (1961) found a pulmonary recirculation time which ranged from 10 to 15 s. In sitting test subjects, CANDER & FORSTER (1959) registered a slightly longer recirculation time of 18 s.

Even more important than the time required for an inhaled gas to return to the lung via the circulation, is the degree of pulmonary recirculation. BAUMAN & GROLLMAN (1930) determined the acetylene concentration in the right ventricle during the breathing of a mixture of acetylene and air. They obtained the blood by direct puncture of the right ventricle. During the period of 13 - 20 s after starting forced inhalation and exhalation of the acetylene/air mixture, the blood acetylene concentration was 5.7% of the alveolar acetylene concentration. Between 25 and 30 s this percentage was 12 and between 33 and 37 s it was 18%.

SANDERS & MORROW (1958) found a pulmonary N_2O recirculation of 5 - 10% during the period of 10 - 30 s after starting breathing of a N_2O-containing gas mixture. These findings were obtained during studies for the detection of intracardiac shunts. Their procedure was the following. A catheter was introduced into the pulmonary artery or the right ventricle and another into a peripheral artery. The patient then started to breathe the N_2O-containing gas mixture. Blood was sampled continuously from the 10th to 30th second and analysed for N_2O content.

WASSERMAN & COMROE (1962) had two subjects inhale a $N_2O + O_2$ mixture to maximum depth and then hold their breath. Blood was sampled from the pulmonary and the radial artery 15 s after starting the respiratory manoeuvre. The N_2O concentration in the blood from the pulmonary artery was only 2% of the N_2O concentration in the blood sampled from the radial artery.

One can infer from the above that several data are available on the time at which pulmonary N_2O recirculation starts, but that information on the amount of recirculating N_2O is more limited. The pertinent publications indicate that, in resting subjects, the pulmonary N_2O recirculation during the first 30 s certainly does not exceed 5 - 10%.

1.2.3.2. Unequal distribution of ventilation-perfusion ratios in the lungs

Determination of PCB by the N_2O body plethysmograph method requires a normal distribution of ventilation-perfusion ratios in the lungs. In the normal lung, different regions differ markedly in the composition of the alveolar gas. WEST & DOLLERY (1960) demonstrated in sitting or standing test subjects that the ventilation-perfusion ratio in the apical regions exceeded that in the basal regions of the lung. Owing to this difference, the alveolar gas in the apical regions differs in composition from that in the basal regions. An end-tidal gas sample involves mixed alveolar gas. In patients with disturbed lung function, the regional differences in ventilation-perfusion ratios are so marked that the mixed alveolar gas exhaled is not of a constant composition. In these cases it is impossible to determine PCB by the N_2O body plethysmograph method.

1.2.3.3. The breathing procedure

Correct execution of the respiratory manoeuvres is difficult for many subjects. This applies in particular to breath-holding with open glottis as required for the LEE & DUBOIS procedure. With the BOSMAN procedure, too, it is often impossible to ensure that the rate of air expiration equals the rate of expiration of the $N_2O + O_2$ mixture.

1.3. Purpose of this study

Having encountered difficulties in subjects to perform correctly the above described breathing procedures, we investigated the possibility of quantitative determination of PCB without special breathing manoeuvres.

Despite correctly executed respiratory manoeuvres we were frequently confronted with improbable PCB values. This prompted us to study a number of factors which play a role in the determination of PCB with the aid of a constant-volume body plethysmograph.

2.1. The body plethysmograph

In this study we used the same body plethysmograph that GIELEN (1971) described in his thesis. This chapter first describes the general properties of the body plethysmograph and then the various modifications made for the determination of PCB (fig. 1).

The apparatus used is manufactured by the firm of Fenyves and Gut (26 Leonardstrasse, Basle, Switzerland). The body plethysmograph has a volume of 470 litres and is designed to accommodate an adult person without difficulty. It has a double wooden wall and a Plexiglas door which can be locked by means of four clamps. It is not absolutely leak-proof, the time constant of the leak being about 60 s. A thermometer and a hygrometer are mounted on the inside of the door. In the wall facing the test subject, a manometer head is mounted which can be replaced by a pneumotachograph if required. Thick-walled plastic tubing connects the manometer head with a differential manometer mounted on top of the body plethysmograph. Apart from the manometer head (or pneumotachograph), a breathing tube perforates this wall of the body plethysmograph. Inside this breathing tube are mounted a pneumotachograph (Fleisch no. 3 : 1 mm H_2O = 0.833 l/s) and an electromagnetic shutter. Both the breathing tube proper and the pneumotachograph are fitted with a heating element. The electromagnetic shutter can be closed as required by means of a button on the control panel. This shutter is used among other things in the determination of the intrathoracic gas volume. The top part of the body plethysmograph contains a reference vessel (volume : 18 l). This reference vessel is called the inside reference vessel. This inside reference vessel can be connected via a length of thick-walled plastic tubing to the manometer head mounted in the wall of the body plethysmograph. The wall of the inside reference vessel can accommodate perforated bolts which ensure a leak to the body plethysmograph with a time constant of 5, 10 or 20 s, but the inside reference vessel can also be completely sealed. Like the body plethysmograph the inside reference vessel has an electromagnetic valve. These valves can be used to equalize the pressures

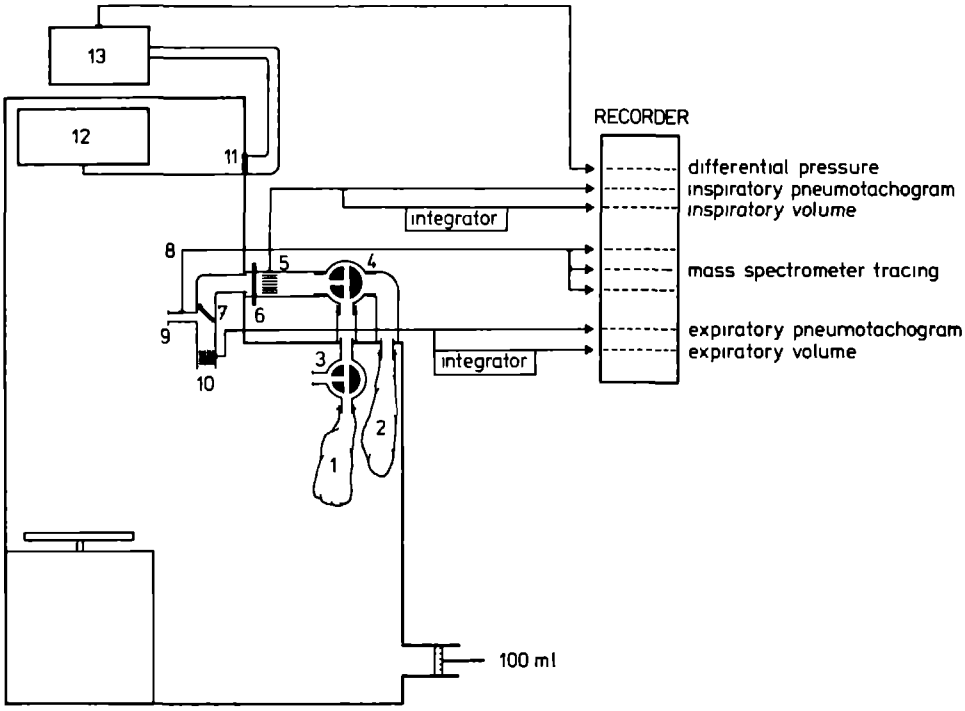

fig. 1. The constant-volume body plethysmograph with modifications for the determination of PCB.

1. = balloon filled with air
2. = balloon filled with $N_2O + O_2$ mixture
3. = three-way stopcock
4. = three-way stopcock
5. = inspiratory pneumotachograph
6. = electromagnetic shutter
7. = one-way valve
8. = sample capillary mass spectrometer
9. = mouthpiece
10. = expiratory pneumotachograph
11. = manometer head
12. = inside reference vessel
13. = differential manometer

in the inside reference vessel and the body plethysmograph to the ambient pressure. The body plethysmograph available to us can be used either as a constant-pressure or as a constant-volume apparatus.

2.1.1. The constant-pressure body plethysmograph

In the constant-pressure body plethysmograph, a pneumotachograph mounted in the wall connects the body plethysmograph with the environment. Changes in the volume of an object within the plethysmograph cause air to flow through the pneumotachograph. Via electrical integration of this pneumotachograph signal, the volume of the air flowing through the pneumotachograph can be measured.

Calibration is effected by pumping a known volume of air into and out of the body plethysmograph, while registering the integrated pneumotachograph signal.

Measurements with a constant-pressure body plethysmograph can be made if the following requirements are met :

- Ambient pressure should not be subject to marked fluctuations while measurements are being made. Fluctuations in ambient pressure cause a flow of air through the pneumotachograph, the direction of flow being dependent on the pressure gradient which at that moment prevails between the body plethysmograph and the environment. VERMEIRE & BUTLER (1968) tried to avoid this problem by registration of the differential pressure between a reference vessel and the environment. The reference vessel communicated with the environment via a number of small apertures, and the signal obtained in this way was employed to correct the pneumotachograph signal. The disadvantage, however, was that the frequency characteristic was flat from DC to only about 2 Hz
- When more protracted measurements are being made (e.g. determination of PCB), the integrator of the pneumotachograph should have a long time constant. In the body plethysmograph available to us we are confronted with a marked integrator drift.

2.1.2. The constant-volume body plethysmograph

In the constant-volume body plethysmograph, changes in the volume of the object within it give rise to changes in pressure. Registration of these changes can be effected by measuring the differential pressure between the body plethysmograph and the inside reference vessel. Alternatively one can measure the differential pressure between the body plethysmograph and the environment. Because of the fairly marked fluctuations in the ambient pressure in the room accommodating our body plethysmograph (up to 0.5 mm H_2O), it was not possible to record the differential pressure between the body plethysmograph and the environment properly. Therefore we made use of a reference vessel placed outside the body plethysmograph. This outside reference vessel was connected with the environment through a small leak. The time constant of this leak was 20 s. In calibrations it may be important to establish whether conditions in the body plethysmograph are isothermic or adiabatic.

In the former case the BOYLE's law ($PV = C$) must be applied when the volume changes corresponding to the pressure changes are calculated. In the latter case the law of POISSON ($PV^K = C$) must be applied.

GIELEN (1971) established that polytropic conditions prevail in our body plethysmograph and that the equation $PV^{1.2} = C$ applies here. Because the same equation applies in calibration, the prevalence of polytropic conditions plays a negligible role in measurements. Calibration is effected as follows 100 ml of air are pumped into and out of the body plethysmograph. Furthermore the following requirements must be met :

1) the calibration volume must correspond to the extent of the changes in the volume of the test object;
2) the rate at which air is pumped into and out of the body plethysmograph should equal the rate at which the volume of the test object changes;
3) the calibration should be carried out as soon as possible after the actual measurement.

2.1.3. The choice between constant-pressure and constant-volume body plethysmograph

In the measurement of PCB we adopted the constant-volume body plethysmograph. The main reason was that the measurements were not disturbed by fluctuations in the ambient pressure. Another reason was the marked integrator drift of the pneumotachograph when a long time constant was used in the constant-pressure set-up. The use of an integrator with a long time constant is - as will be discussed later - mandatory for the determination of PCB.

2.2. The mass spectrometer

For analysis of the respiratory gases we made use of an eight-channel Centronic quaduprole mass spectrometer (Twentieth Century Electronics Ltd, New Addington, Croydon CR9 OBG, England). In the high-vacuum section of this type of mass spectrometer, four electrodes are arranged in parallel. Via these electrodes potential modulations of two types are transmitted, firstly a RF potential signal of increasing amplitude and with a phase difference of 180^{o} between each electrode pair and secondly an increasing direct current. Of the ionized gas mixture only ions with a specific mass-to-charge ratio reach the detector at any given moment. The output of the detector is proportional to the concentration of the type of ions measured at that moment. The mass spectrometer has a mass-to-charge ratio of 2 - 100 amu (atom mass unit). The response time is less than 100 ms for 0 - 90% of a square input of dry air. The inlet sample capillary is 1000 mm long, and its transition time is 150 ms. The sample rate is 25 ml/min. This capillary can be heated up to 100^{o}C. In the arrangement for determining PCB the sample capillary passed through the side-wall of the body plethysmograph, the inlet being sealed air-tight. The sample inlet was fixed to the mouthpiece used by the test subject.

2.3. The recorder

We used a Gould-Brush Recorder type 481. This is a general purpose-direct-writing recorder with eight channels that have a plotting width of 40 mm.

Its sensitivity varies from 1 mV to 10 V per division. The frequency response is flat from DC to 40 HZ at full scale, and to 100 Hz at 10 divisions (about 20% of full scale). The plotting system is of the pressurized ink type. The paper speed can be varied in 12 steps from 0.05 mm/s to 200 mm/s.

2.4. Modifications of the apparatus for determination of PCB

In the course of the study it was found necessary to keep the inspiratory volume constant, both when breathing air and when breathing the $N_2O + O_2$ mixture. To ensure this, use was made of the pneumotachograph in the breathing tube, the electromagnetic shutter and a one-way valve.

2.4.1. The pneumotachograph

A pneumotachograph can be used to measure a gas flow. The principle is based on measuring the pressure decay which occurs when a gas flow passes a resistance built into the system. The law of POISEUILLE applies to laminar flow. This law reads :

$$V/t = (P_1 - P_2) \frac{\pi r^4}{8 \eta l}$$

V = volume
t = time
r = radius of tube
η = viscosity
l = length of tube
$P_1 - P_2$ = pressure gradient between two ends of the tube.

In laminar flow the pressure decay is proportional to the viscosity of the gas and independent of the density of the gas. In turbulent flow, however, the density of the gas does play a role in determining the pressure gradient, whereas viscosity does not. For adequate use of the pneumotachograph the maximal flow (i.e. the flow which just avoids turbulence) must not be exceeded.

If turbulence nevertheless occurs, the pneumotachograph reading for flow is too high, and there is no linear relation between flow and pressure decay registered via the pneumotachograph. The following factors should be taken into account when working with the pneumotachograph :

1) changes in the temperature of the passing gas cause changes in its volume as well as in its viscosity;
2) changes in the composition of the passing gas cause changes in its viscosity and thus influence the pressure signal registered by the pneumotachograph;
3) the composition of the standard gas should be identical to that of the test gas.

The factors mentioned sub 1) and 2) are of importance when a test subject inhales and exhales through a pneumotachograph. GRENVIK (1966) emphasized that it follows from the gas laws that, at 20°C, an increase in volume by 0.34% occurs per centigrade increase in temperature. He also mentioned a rise in viscosity by 0.17% per centigrade increase in temperature.

Regarding the composition of the standard gas one must bear in mind that significant errors may occur when different gases are used in the determination. To illustrate this : when the standard gas is air while the test gas is $N_2O + O_2$ mixture (which contains 80% N_2O), the error made at calibration would amount to about 20%, since these gas mixtures differ markedly in viscosity (table 1).

Table 1. Viscosity of some gases (according to GRENVIK)

gas	viscosity at 20°C (millipoiseuilles)	percentual volume error (air as standard gas)
air	0.0183	0
O_2	0.020	+ 9.4
CO_2	0.0148	-23.6
N_2	0.0175	- 4.6
N_2O	0.0146	-25.3

The differential pressure registered by the pneumotachograph can be converted to an electrical signal. When this signal is guided through an integrator, the output of the integrator is a measure of the gas volume passing through the pneumotachograph.

2.4.2. Constant inspiratory volume

The following electrical circuiting was used to ensure a constant inspiratory volume. The pneumotachograph signal was guided into an integrator. The signal thus obtained was compared with a signal originating from an adjustable power source. The moment these two signals are equal, an impulse is released. This impulse is amplified and prolonged by a one-shot, which in turn releases the following signals (cf. fig. 2) :

- a signal which operates the relay controlling the closure of the shutter placed between inspiratory pneumotachograph and one-way valve
- a signal which returns the integrator to the baseline position
- a signal which causes a lamp to burn as long as the shutter is closed.

Another pneumotachograph is mounted on the expiratory side of the one-way valve, and the signal from this pneumotachograph can also be integrated.

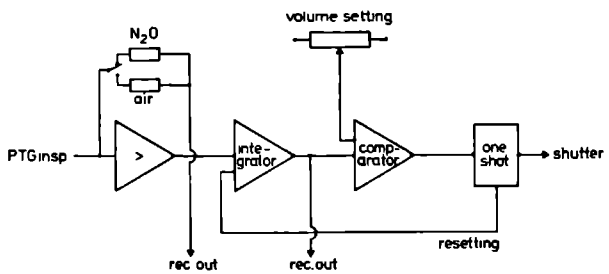

fig. 2. Electronic circuit for constant inspiratory volume.

2.4.3. Correction of the inspiratory pneumotachograph for N_2O breathing

As already mentioned, the sensitivity of the pneumotachograph is not identical for air and N_2O. To ensure that the volume remains constant after switching from air to $N_2O + O_2$ mixture, a modification was made to

the system described above. The following method was used : a spirograph was filled with air and connected with the inspiratory pneumotachograph. A weight was placed upon the spirograph bell so that air was forced through the pneumotachograph.
The following parameters were registered :

- pneumotachogram
- integrated pneumotachogram
- volume of air passing through the pneumotachograph as registered by the spirograph tracing.

Once the pre-set volume was attained, the shutter closed. One could see this clearly on the spirograph tracing. After repeating the procedure several times (making sure that the spirograph excursions were constant), the spirograph was filled with a $N_2O + O_2$ mixture containing 60 - 80% N_2O, 20% O_2 and 0 - 20% air. At 80% N_2O the shutter closed at a volume which was 20% higher that that at which it closed with air. The components of modification were chosen so that during perfusion with the $N_2O + O_2$ + air mixture, the shutter closed at the same volume as with air alone. The values of the components were determined at 60, 65, 70, 75 and 80% N_2O. (cf. fig. 2).

2.4.4. One-way valve, expiratory pneumotachograph and mouthpiece

Within the body plethysmograph, the breathing tube connects with a one-way valve which has a very low resistance to passing gas. This resistance is such that a pressure gradient of 4 mm H_2O occurs in the inspiratory part of the one-way valve at an air flow of 0.3 l/s. For the expiratory part the resistance at the same air flow is 3.8 mm H_2O.

On the expiratory side of the valve a second pneumotachograph registers expiratory flow. This pneumotachograph is connected by thick-walled plastic tubing with a differential manometer mounted outside the body plethysmograph. The sample tube of the mass spectrometer is attached to the mouthpiece of the one-way valve. The site at which the sample tube passes through the wall of the plethysmograph is sealed air-tight. The

same applies to all other sites at which tubing passes through the wall of the plethysmograph. This arrangement makes it possible to have a test subject breathe air from the body plethysmograph while the inspiratory volume remains constant. This volume remains constant also when switching is done from air to $N_2O + O_2$ mixture. The expiratory air is forced back into the plethysmograph via the one-way valve. By adjusting the three-way stopcock the test subject can inhale air or another gas mixture from a plastic balloon suspended within the body plethysmograph.

By adjusting another stopcock inside the body plethysmograph, the test subject can be made to inhale air or another gas mixture from a second plastic balloon suspended in the body plethysmograph. The plastic balloons have a low compliance. In this arrangement the following registrations can be made :

1. Inspiratory pneumotachogram and volume;
2. Expiratory pneumotachogram;
3. Differential pressure between the body plethysmograph and the inside reference vessel;
4. Differential pressure between the body plethysmograph and the outside reference vessel;
5. Differential pressure between the inside and the outside reference vessel;
6. Composition of respiratory gases (mass spectrometer).

CHAPTER 3. SOME PHYSICAL PROPERTIES OF THE CONSTANT-VOLUME BODY PLETHYSMOGRAPH

3.1. Introduction

Unlike other determinations made with the aid of the body plethysmograph (e.g. intrathoracic gas volume and respiratory work) the determination of PCB takes a relatively long time. For reliable determination of PCB it is therefore necessary to have an exact knowledge of the nature of the slow pressure changes which occur while a test subject is in the body plethysmograph. A test subject releases energy into the body plethysmograph in two forms : heat and water vapour. We studied the course of pressure changes in the body plethysmograph while energy was being supplied in the form of heat and water vapour.

3.2. The course of pressure in the body plethysmograph and the reference vessel during heat production

For registration of these pressure changes we used the following test arrangement. A lamp was placed on the bench which normally accommodates the test subject in the body plethysmograph. The body plethysmograph was closed and the lamp was switched on. We consecutively used three bulbs of increasing wattage : 75, 100 en 150 watt (W).
Values registered were :

1. differential pressure between the body plethysmograph and the outside reference vessel;
2. differential pressure between the inside and the outside reference vessel;
3. differential pressure between the body plethysmograph and the inside reference vessel;
4. temperature inside the body plethysmograph.

3.2.1. The course of differential pressure between the body plethysmograph and the outside reference vessel

When the body plethysmograph is closed and the lamp is switched on, the

differential pressure between the body plethysmograph and the outside reference vessel begins to increase. When the differential pressure between the body plethysmograph and the outside reference vessel is plotted against time, the following curve is obtained.

Progressive elevation of the curve begins 5 s after the lamp is switched on. Between 12 and 24 s after switch-on the slope of the curve is maximal. The slope gradually diminishes between 24 and 100 s after switch-on, and the curve attains a maximum about 100 s after switch-on, whereupon it takes a declining course. The curve shows a slight notch due to a slight change in the slope about 200 s after switching on, and then continues on an approximately linear course (fig. 3). The temperature rise after switching on the 150 W lamp amounted to 0.25°C/min. For the 100 and 75 W lamp this was 0.15 and 0.10°C/min respectively.

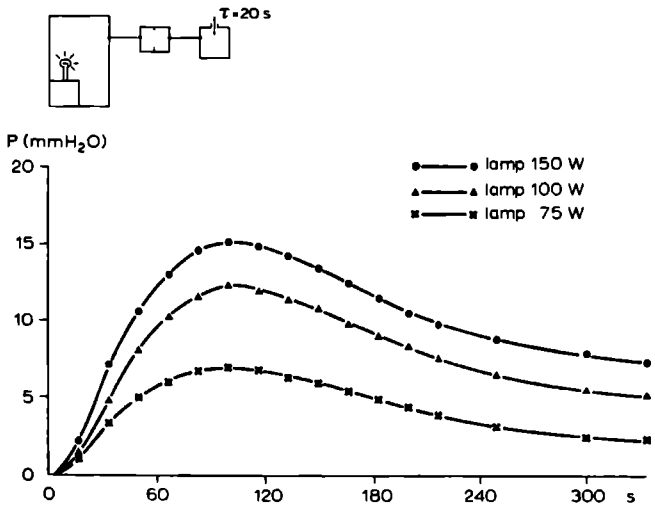

fig. 3. The course of the differential pressure between the body plethysmograph and the outside reference vessel after switching on lamps of 75, 100 and 150 W. Ordinate : pressure (P), abscissa : time (s).

Comparison of the curves obtained with 75, 100 and 150 W lamps shows that the times at which changes in the slope occur, agree in that the maxima of the curves coincide in time (100 s after switch-on). The absolute values

of the slopes and the maxima, however, differ. At a time constant of 60 s for the leak between the body plethysmograph and the environment, a maximum pressure of 15.2 mm H_2O is attained with a 150 W lamp; maxima attained with a 100 W, and a 75 W lamp are 12.4 and 7.1 mm H_2O respectively. If one waits long enough one can see the pressure return to atmospheric level, for there is no longer any pressure gradient when there is no longer any change in temperature. This situation prevails when heat supply by the lamp and heat release from the body plethysmograph to the environment are equal. The heat supply by the lamp per unit of time is constant. The heat release is dependent on the thermic properties of the body plethysmograph. When the lamp is switched off, the pressure in the body plethysmograph diminishes immediately (fig. 4).

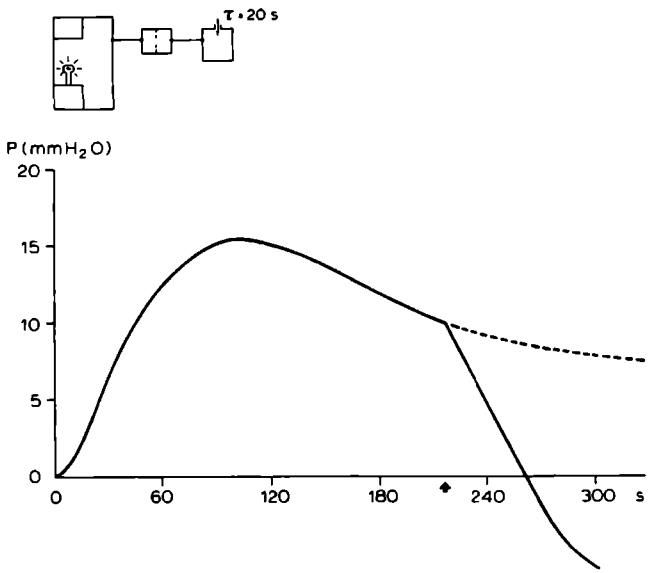

fig. 4. Differential pressure between the body plethysmograph and the outside reference vessel after switching on a 150 W lamp. The arrow indicates the moment when the lamp is switched off. Note the rapid pressure drop and the negative value of the differential pressure.
Ordinate : pressure (P), abscissa : time (s).

The decrease in fact continues until the differential pressure between the

body plethysmograph and the outside reference vessel assumes even a negative value. A minimum of - 7 mm H_2O is attained 80 s after switching off the 150 W lamp. The corresponding values with the 100 W and the 75 W lamp are - 4.5 mm H_2O and - 3.5 mm H_2O respectively.

3.2.2. The course of differential pressure between the inside and the outside reference vessel

In order to measure the differential pressure between the inside and the outside reference vessel, one side of the differential manometer was connected with the inside reference vessel, the other side being left open to the environment via the above-described outside reference vessel. The body plethysmograph was closed and a lamp was switched on. This was followed by registration of a curve of differential pressure against time. We used bulbs of 150, 100 and 75 W.

During the first 15 s after switching on the curve takes a virtually horizontal course. A brief transient change comes next in the slope, whereupon the curve takes a nearly linear course in time. 240 s after switching on the differential pressure is 9 mm H_2O with the 150 W lamp, 6.2 mm H_2O with the 100 W lamp, and 3.2 mm H_2O with the 75 W lamp (fig. 5).
A slight change in the slope occurs about 6 min after switching on, reducing the steepness of the curve. The differential pressure 10 min after switch-on are 20, 12 and 5 mm H_2O with the 150, 100 and 75 W lamp, respectively.

After the ventilating valve is used to equalize the pressure of the inside reference vessel and the environment the inside reference vessel is closed again. The pressure curve then shows the following course. During the first 45 s the slope of the curve exceeds that during the next period. After 45 s the slope changes so that the curve takes a less steep course. The curve then continues on about the same course as that described after switching on the lamp.

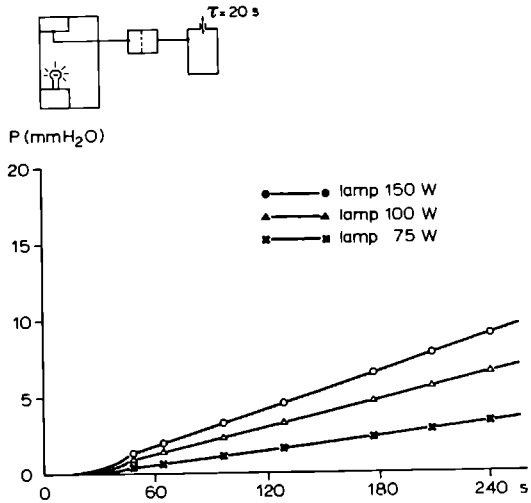

fig. 5. The course of the differential pressure between the inside and the outside reference vessel after switching on lamps of 75, 100 and 150 W. Ordinate : pressure (P), abscissa : time (s).

3.2.3. The course of differential pressure between the body plethysmograph and the inside reference vessel

The curve which indicates the course of differential pressure between the body plethysmograph and the inside reference vessel, can be predicted on the basis of the data obtained by registration of the differential pressure between the body plethysmograph and the outside reference vessel and that between the inside and the outside reference vessel (fig. 6).
The curve shows an increase in pressure 5 s after switching on the 150 W lamp; 85 s after switch-on the maximum differential pressure between the body plethysmograph and the inside reference vessel is attained. This is 12 mm H_2O. The curve then assumes a declining course, exactly as it does when the differential pressure between the body plethysmograph and the outside reference vessel is measured. The change in the slope of the curve also corresponds with that in the curve which indicates the differential pressure between the body plethysmograph and the outside reference vessel.

The differential pressure between the body plethysmograph and the inside reference vessel 240 s after 'switch-on' is 0. After 300 s this differential pressure is - 3.5 mm H_2O (fig. 6).

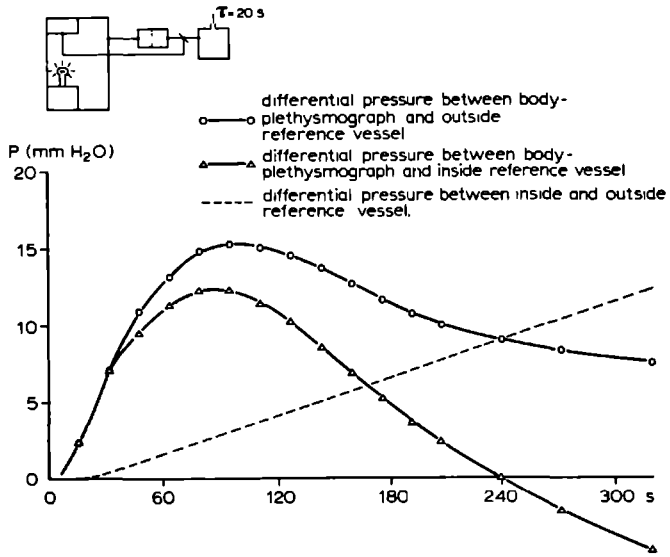

fig. 6. The course of the differential pressure between the body plethysmograph and the inside reference vessel after switching on a lamp of 150 W. Ordinate : pressure (P), abscissa : time (s).

3.2.4. Comments

3.2.4.1. The course of differential pressure between the body plethysmograph and the outside reference vessel

The curve can be divided into a rapidly rising segment, a maximum and a slowly declining segment. Although the heat production in the body plethysmograph is constant - and the increase in the temperature takes a virtually linear course in time - the shape of the curve is complicated. Factors determining the course of pressure changes are the following:

1. Heat production by the lamp. Apart from the first few seconds after switching on the lamp, its heat production (and therefore the release

of energy into the body plethysmograph) can be assumed to be constant;
2. The time constant of the leak between the body plethysmograph and the environment;
3. The heat release from the body plethysmograph to the environment;
4. The heat capacity of the body plethysmograph.

During the first segment of the curve (the steep rise), the heat production by the lamp exceeds the energy release from the body plethysmograph to the environment. During the maximum elevation of the curve the factor which causes an increase in pressure balances the factors which cause a decrease in pressure. At that time the increase in pressure which should have been caused by the rise in temperature due to the heat production by the lamp, equals the decrease in pressure which should have resulted from the heat release from the body plethysmograph to the environment and the time constant of the leak. The fact that the pressure curve then takes a declining course can only be explained by assuming that the energy release from the body plethysmograph to the environment increases. The other factors may be assumed to remain constant.

The virtually immediate decrease in pressure after switching off the lamp is explained by the cessation of the heat production. However, the factors which promote a decrease in pressure continue to exert their influence, because both leakage of air and heat release from the body plethysmograph continue. This explains why the differential pressure between the body plethysmograph and the outside reference vessel assumes a negative value. The curve reaches its lowest point (in fig. 4 to the right; not shown) when the factor which causes a decrease in pressure is balanced by the factors which cause an increase in pressure. The fact that the pressure curve rises again is due to a decrease in the energy release from the body plethysmograph to the environment.

3.2.4.2. The course of differential pressure between the inside and the outside reference vessel

The lamp heats the reference vessel suspended in the top part of the body plethysmograph in two ways :
1) by convection; air heated by the lamp rises;

2) by radiation.

Since the wall of the inside reference vessel has an insulating function, the air within it initially shows no increase in temperature. In the curve, this is reflected by the horizontal course of the initial segment, which lasts 15 s. The air within the inside reference vessel is then heated as a result of heat conduction via the wall. The increase in differential pressure between the inside and the outside reference vessel per unit of time is virtually constant. This is explained by the fact that the inside reference vessel is sealed off from the body plethysmograph, while the heat supply per unit of time is likewise constant. In the curve, this is reflected by the segment which takes a linear course. Owing to this linear course, the change in the slope of the curve which indicates the course of differential pressure between the body plethysmograph and the inside reference vessel is identical to that of the curve which indicates the course of differential pressure between the body plethysmograph and the outside reference vessel.

3.2.5. The use of the ventilating valve during protracted determinations in the body plethysmograph

Let us now consider how the use of the ventilating valve influences the course of the curve which indicates the differential pressure between the body plethysmograph and the inside reference vessel. For continuous registration of the curve after switching on a lamp the ventilating valve must be used if the absolute value of differential pressure exceeds the measuring range of the manometer. We compared the course of the curve obtained after switching on a 150 W lamp while using a manometer with a range of 5 mm H_2O, with that obtained while using a manometer with a range of 20 mm H_2O. The curves obtained in these two manometer ranges are of quite different shape as demonstrated in fig. 7. Using a manometer with a range of 5 mm H_2O the slope of the curve was relatively steep till the moment that the pressure curve as obtained by using a manometer with a range of 20 mm H_2O, was at its maximum. The steepness of the slope then gradually diminished. Finally, the curves coincided 240 s after 'switch-on'. It is to be noted that the change in the slope of the curve obtained

using a manometer with a range of 5 mm H_2O was 80^0 between 120 and 240 s after 'switch-on'. During the same period this was only 8^0 when using a manometer with a range of 20 mm H_2O.

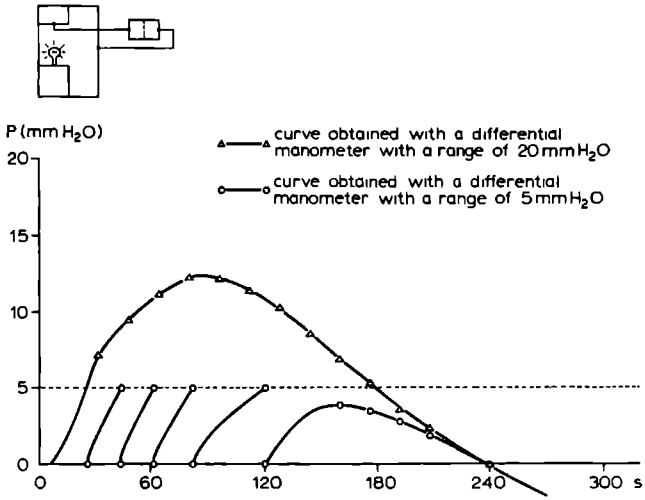

fig. 7. Differential pressure between the body plethysmograph and the inside reference vessel after switching on a 150 W lamp. Ordinate : pressure (P), abscissa : time (s).
Note the completely different shape of the curve when the ventilating valve is used. For further explanation see text.

In the course of the study it was established that intermittent heat release from the relay to the inside reference vessel occurs when the ventilating valve is used frequently. When the ventilating valve is open, the relay is operated and releases heat to the inside reference vessel. As the valve is closed, the relay is released and the inside reference vessel cools. As a result, the differential pressure between the inside and the outside reference vessel decreases. The extent of this change in differential pressure depends on the lenght of time during which the ventilating valve remained open. If it remained open during 25 s, then the maximum change in differential pressure between the inside and the outside reference vessel after closing is 0.75 mm H_2O/min; if it remained open during 5 min, then the maximum change is 1.2 mm H_2O/min. We think that during the determinations which take tens of seconds, the course of

the pressure curve of the body plethysmograph due to heating and humidification should be entirely predictable. When the ventilating valve is used, this cannot be accomplished. The arguments are the following :

1. When the valve is used, more marked changes can occur in the slope of the curve during a given period than when the valve is not used;
2. The course of the curve which indicates the differential pressure between the inside and the outside reference vessel begins to deviate from the linear course when the valve is used. Here, the relay has a disturbing effect on the reading.

During determination of the differential pressure between the body plethysmograph and the inside reference vessel, the pressure in the latter should remain constant. If this is impossible, the pressure change per unit of time in the inside reference vessel should be constant. In our body plethysmograph this can only be ensured by avoiding the use of the ventilating valve during a determination.

3.3. The course of pressure in the body plethysmograph with increasing water vapour pressure

Because a test subject releases water vapour as well as heat to the body plethysmograph, we studied the course of pressure in the body plethysmograph with increasing water vapour pressure. A container filled with water was placed inside the body plethysmograph. The water was stirred by means of a paddle, activated by a small electric motor. The heat release of this motor invalidated any investigation on the effect of the rise of the water vapour pressure inside the body plethysmograph. Since we have found it impossible to increase the water vapour pressure without changing the heat release in the body plethysmograph, we attempted to simulate the effect of water vapour releases by insufflating a constant volume of air into the body plethysmograph. The water vapour release from a test subject via respiration and perspiration is known to amount to about 600 ml/min under basal conditions (WRIGHT, 1961). The differential pressure between the body plethysmograph and the inside reference vessel was registered during insufflation with 300, 600 and 900 ml air per minute. The course of the curve which indicates the differential pressure proved to be approximately exponential (fig. 8a). The thermic effects and related

pressure changes which occurred during air insufflation were ignored. The maximum value of the pressure in the body plethysmograph (P_{max}) is a function of the amount of air insufflated per unit of time (F), the ambient pressure (P_B) and the conductance (K) of the leak from the body plethysmograph to the environment.

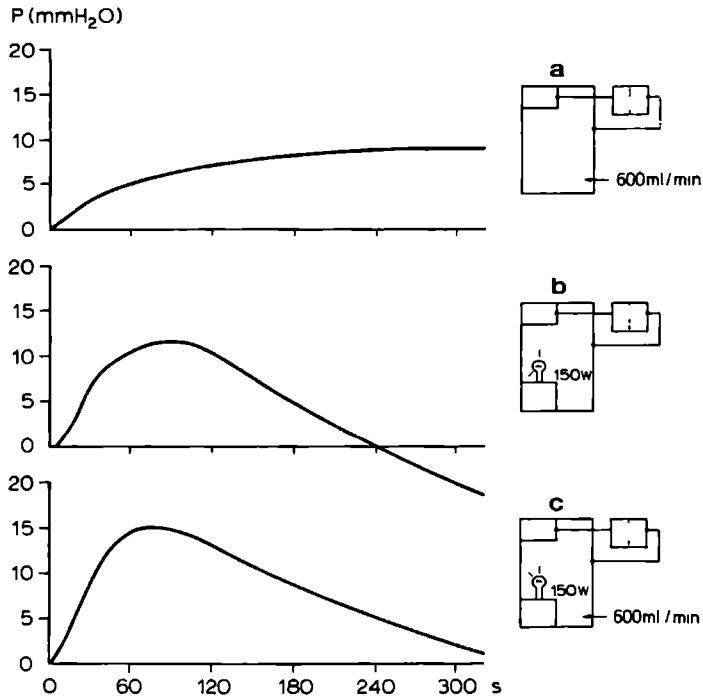

fig. 8. Differential pressure between the body plethysmograph and the inside reference vessel. Ordinate : pressure (P), abscissa : time (s).

a. pressure course during air insufflation of 600 ml/min into the body plethysmograph
b. pressure course after switching on a 150 W lamp
c. pressure course during simultaneous insufflation of air and switching on a 150 W lamp.

This can be expressed in the following equation :

$$P_{max} = P_B + \frac{F}{K}$$

3.4. The course of pressure in the body plethysmograph upon simultaneous production of heat and water vapour

If the subject's heat production is assumed to be 150 W and the water vapour release is assumed to be 600 ml/min, the course of the curve which indicates differential pressure between the body plethysmograph and the outside reference vessel can be simulated by insufflation with 600 ml air per minute (fig. 8 b.c), while at the same time a 150 W lamp is switched on inside the body plethysmograph. The curve thus obtained is a composite of the curves obtained during heat production inside the body plethysmograph and during insufflation of air into the body plethysmograph respectively. In this case the differential pressure between the body plethysmograph and the outside reference vessel is maintained at a higher level than after switching on the lamp alone. The usefulness of measuring differential pressure between the body plethysmograph and the inside reference vessel now becomes apparent. Due to the relatively high pressure in the inside reference vessel (resulting from the heating of the air inside it) the differential pressure between the body plethysmograph and the inside reference vessel is significantly lower than that between the body plethysmograph and the outside reference vessel. Consequently the differential pressure between the body plethysmograph and the inside reference vessel approaches the range of the differential manometer sooner.

3.5. Summary

1. When the body plethysmograph is heated by means of a lamp placed inside it, the curve which indicates the differential pressure between the body plethysmograph and the outside reference vessel takes a characteristic course : a rapidly rising initial segment, a maximum followed by a slight decline, and a final segment which has a virtually linear course.

2. When the body plethysmograph is heated by means of a lamp placed inside it, the curve which indicates the differential pressure between the inside and the outside reference vessel, takes a linear course.

3. The use of the ventilating valve during protracted determinations can influence the predictability of the course of the pressure curve :
   - due to marked changes in the slope of the pressure curve
   - due to deviations from the linear in the course of the curve indicating the differential pressure between the inside and the outside reference vessel due to heat release from the relay in the inside reference vessel.

4. When water vapour production inside the body plethysmograph is simulated by air insufflation, the curve which indicates the course of the differential pressure between the body plethysmograph and the outside reference vessel takes a simple, approximately exponential course.

5. The advantage of measuring the differential pressure between the body plethysmograph and the inside reference vessel is that registration of the pressure curve can commence earlier.

4.1. Introduction

In order to measure the volume of N_2O taken up by the pulmonary capillary blood flow per unit of time, the pressure course in the body plethysmograph during air breathing must be compared with that during breathing a mixture of N_2O and O_2. In this comparison there should be only one variable : breathing of the $N_2O + O_2$ mixture instead of air. All other factors which influence the pressure course in the body plethysmograph, should be kept constant throughout the determination. These factors are discussed in the following sections.

4.2. The course of pressure while a subject is in the body plethysmograph

The course of the curve which indicates the differential pressure between the body plethysmograph and the outside reference vessel while a subject is inside, is the resultant of :

1. the change in pressure which results from the increase in temperature and water vapour pressure in the body plethysmograph;
2. the intrathoracic pressure changes related to the respiratory cycle;
3. the physical properties of the body plethysmograph.

The curve which indicates the course of pressure can be divided into a slow component (or drift) and a rapid component which coincides with respiration. Although the division of the curve into two components may seem rather arbitrary, it is nevertheless justified because it contributes to a better understanding of the factors which determine the course of pressure (fig. 9).

The slow component of the curve is largely determined by :

- a change in pressure due to heat release from the skin by the test subject via radiation and convection
- a change in pressure due to release of water vapour through the skin
- an increase in pressure due to heating and humidification of respiratory

air

- a change in pressure resulting from the respiratory quotient.

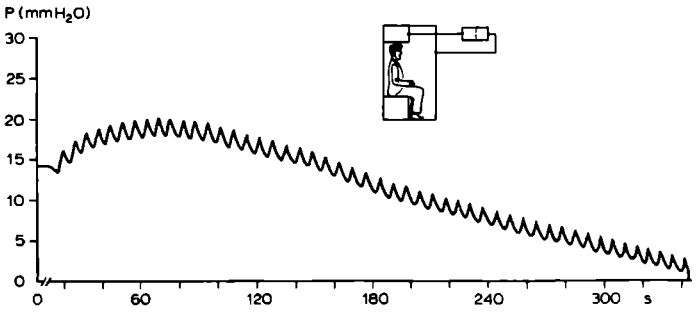

fig. 9. Differential pressure between the body plethysmograph and the inside reference vessel. Ordinate : pressure (P), abscissa : time (s). Pressure course with a subject breathing a constant inspiratory volume. Note the resemblance of the slow component with the curve shown in fig. 8c.

If the curve which indicates the course of differential pressure between the body plethysmograph and the inside reference vessel is registered while a subject is inside, then the slow component of this curve is unmistakably similar to the curve obtained during air insufflation into the body plethysmograph after a lamp is switched on inside. The slow component attains a maximum after about 80 s; the level of this maximum depends on the heat and water vapour release from the subject. Obviously there are substantial interindividual differences in this respect. After reaching its maximum the curve continues on a slowly delcining course. A slight notch occurs after about 180 s, whereupon the slow component continues on a practically linear declining course.

The literature contains only scanty data on the course of the slow component of the curve. QUANJER (1971) referred to an 'exponential rise' of the pressure in the body plethysmograph once a subject has entered it. This did not occur in our set-up.

The rapid component of the curve can be divided into an ascending segment, related to the inspiratory phase, and a descending segment which is related to the expiratory phase. The slope of the inspiratory (ascending) segment is determined by :

- the rate at which intrathoracic pressure changes during the inspiratory phase
- the difference in temperature and water vapour pressure between the air inhaled from the body plethysmograph and that in the lungs.

At the end of the inspiratory phase the pressure curve attains a maximum. This peak height is determined by :

- the inspiratory volume
- the difference in temperature and water vapour pressure between the air inhaled from the body plethysmograph and that in the lungs.

The slope of the expiratory (descending) segment is determined by :

- the rate at which intrathoracic pressure changes during the expiratory phase.

At the end of the expiratory phase the pressure curve attains a minimum, the level of which is determined by the expiratory volume.
The values of the four above-mentioned features of the rapid component are otherwise determined by :

- the intrathoracic gas volume
- the volume of the body plethysmograph
- the time constant of the leak from the body plethysmograph to the environment.

BARGETON (1967) introduced an equation which indicates the relation between the pressure change in the body plethysmograph during the respiratory cycle and the above-mentioned factors :

$$P_k = aV_i + b (V_o + V_i) u,$$

in which :

a and b = constants related to temperature, water vapour pressure in and volume of the body plethysmograph

P_k = change of pressure in the body plethysmograph during the respiratory cycle

V_i = inspiratory volume

V_o = intrathoracic gas volume

u = maximum difference between pressure in the body plethysmograph and intrathoracic pressure.

This equation assumes that ideal gases are involved. The RQ effect is ignored. It is assumed that one state of equilibrium is instantaneously replaced by another. The time constant of the leak from the body plethysmograph to the environment is likewise ignored. The equation shows that the pressure change in the body plethysmograph during the respiratory cycle is dependent on three variables. If pressure changes of constant value are to be ensured in the body plethysmograph during respiration, the following requirements must be met :

- the inspiratory volume of the consecutive respirations should remain constant
- all expirations must be made to the same depth, i.e. the intrathoracic gas volume at end-expiration should remain constant
- temperature and water vapour pressure of the inspiratory gas mixture (or air) should remain constant during the consecutive respirations.

4.3. Study of factors influencing the course of pressure

We studied the influence of the following factors on the course of the curve which indicates the differential pressure between the body plethysmograph and the inside reference vessel :

- inspiratory volume
- inspiratory water vapour pressure
- temperature of inspiratory gas
- rate of expiration.

4.3.1. Inspiratory volume

With the aid of the one-way valve described earlier, the subject was supplied with an inspiratory volume of constant size. The subject exhaled normally to the depth which he (she) usually attained. He was asked to keep the intervals between consecutive inhalations constant. Subsequently he breathed at an inspiratory volume which equalled the normal tidal volume. During this procedure the subject did not remain in the body plethysmograph longer than 5 min. Some time later the test was repeated at an inspiratory volume twice as large as the normal tidal volume. Finally the test was repeated at an inspiratory volume three times the tidal volume. The values registered were : differential pressure between the body plethysmograph and the inside reference vessel, inspiratory volume and inspiratory and expiratory pneumotachogram.
Result :
The curves obtained in this manner prove to show a smooth, regular course. The course taken by the slow component is shown in fig. 9. In the rapid component the amplitude and the slope of the ascending segment are reproduced in consecutive respiratory cycles. The same applies to the descending segment, which corresponds to the expiratory phase.

The respiratory rate decreases as a subject at rest starts breathing a larger inspiratory volume. Most subjects get used to breathing at the same inspiratory flow. Consequently the slope of the inspiratory segment remains about the same when breathing a larger inspiratory volume, but the amplitude of the rapid component increases of course. However, the course of the slow component of the pressure curve remains the same. The crucial point is that the curves obtained during respiration at a constant inspiratory volume take a predictable and reproducible course.

4.3.2. Inspiratory water vapour pressure

4.3.2.1. Test arrangement

In order to establish the influence of the inspiratory water vapour pressure the subject was asked to enter the body plethysmograph and to breathe at an inspiratory volume of twice the tidal volume. After

3 min the three-way stopcock was used to connect the subject to a balloon filled with dry air. He inhaled six times from this balloon and then returned to breathing the air in the body plethysmograph. An eight-channel recorder was used to register the following parameters :

- the course of differential pressure between the body plethysmograph and the inside reference vessel
- the inspiratory pneumotachogram
- the expiratory pneumotachogram
- the water vapour and oxygen pressure of the respiratory gas as sampled by the capillary of the mass spectrometer
- the temperature of the air in the balloon and in the body plethysmograph (a suitable thermistor was used for this purpose)
- the relative humidity in the body plethysmograph.

4.3.2.2. Results

Breathing dry air after breathing relatively humid air from the body plethysmograph has a distinct effect on the course of both the slow and the rapid component of the pressure curve (fig. 10). After switching to dry air the slow component starts rising from the previous level. In the rapid component the slope of the inspiratory (ascending) segment and its peak height increase. In the expiratory (descending) segment the slope also increases, though less than in the inspiratory segment. Consequently the final lowest point of the rapid component, or reversal point to the next inspiratory segment, is on a higher level than that of the preceding respiratory cycle.

When after breathing dry air the subject resumes breathing air from the body plethysmograph, the course of the slow component of the curve immediately declines. In the rapid component the slope between ascending segment and abscissa diminishes but remains larger than it was before the subject breathed dry air. The same applies to the descending segment of the rapid component. The registrations of the inspiratory and expiratory pneumotachogram show a constant pattern throughout. Registration of the water vapour pressure and the oxygen pressure reveals a marked difference in value after the switch-over. The difference in the oxygen pressure is

caused by the higher partial oxygen pressure of dry air in the balloon, as compared to the humid air in the body plethysmograph. The temperature of the air in the balloon is identical to that in the body plethysmograph : 24°C. The relative humidity in the body plethysmograph is 72%.

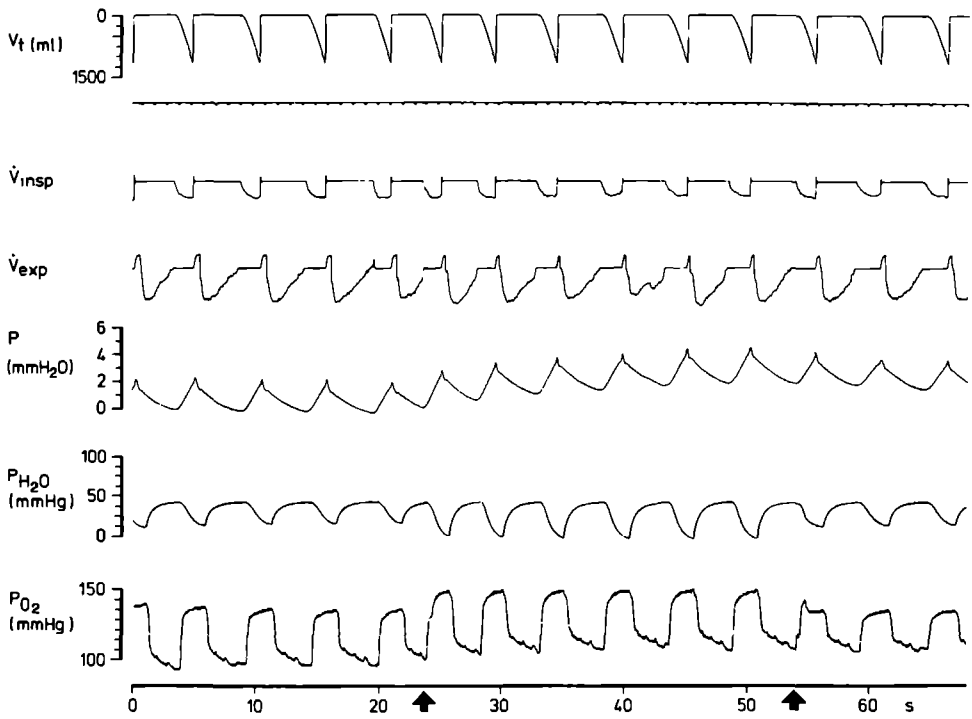

fig. 10. Effect of a change in humidity of the inspired air on the pressure course in the body plethysmograph. The first arrow shows where the change was made from breathing humid air to dry air. The second arrow shows where dry air breathing was followed by breathing humid air. For explanation see text. From top to bottom : tidal volume (V_t), inspiratory pneumotachogram ($\dot{V}_{insp}$), expiratory pneumotachogram ($\dot{V}_{exp}$), differential pressure between the body plethysmograph and the inside reference vessel, water vapour pressure (P_{H_2O}) and oxygen pressure (P_{O_2}) of the respiratory air.

4.3.2.3. Discussion

It is apparent from the above that the difference in water vapour pressure in the inspiratory air exerts a striking influence on the course of the differential pressure between the body plethysmograph and the inside reference vessel. This is caused by the relatively marked increase in volume of the inspiratory air while the subject is breathing from the balloon filled with dry air. At a temperature of 24°C and a relative humidity of 72% in the body plethysmograph, the water vapour pressure is 17.3 mm Hg. Given an inspiratory volume of 1000 ml and a barometer reading of 760 mm Hg, the increase in volume due to humidification per respiratory cycle is (47 - 17.3)/ 760 x 1000 ml = 39 ml. The increase in volume while breathing dry air is (47 - 0)/ 760 x 1000 ml = 62 ml.

The switch-over to breathing dry air from the balloon after breathing air from the body plethysmograph therefore gives rise to a marked increase in pressure during the inspiratory phase. The shape of the curve changes according to the difference in water vapour pressure between the air in the body plethysmograph and that in the balloon.

The respiratory air is humidified during inspiration. Since the inspiratory air becomes drier the slope of the ascending segment of the rapid component increases (always provided that the inspiratory flow pattern is constant during the consecutive respiratory cycles). The fact that the slope of the descending (expiratory) segment of the curve also increases, is explained by the increase in differential pressure between the body plethysmograph and the environment. As a result of this higher differential pressure, the influence of the leak from the body plethysmograph to the environment is more marked and consequently the expiratory segment of the curve takes a steeper course.

Let us consider in this context the influence of the time constant of the leak (τ_1) from the body plethysmograph to the environment on the course of the curve, applying the law of BOYLE & GAY-LUSSAC.

$$PV = nRT,$$

in which

P = pressure
V = volume
n = number of gas molecules
R = gas constant
T = absolute temperature.

If in case of a completely sealed constant-volume body plethysmograph ($\tau_1 \rightarrow \infty$) we assume that the temperature of the humid air equals that of the dry air, then

$$P \sim n$$

Let the increase in pressure in the body plethysmograph during inhalation of dry air be P_1 and that during inhalation of humid air P_2. Let the increase in the number of H_2O molecules in the gas phase in the lungs be n_1 and n_2, respectively. Since more H_2O molecules are added to dry air than to humid air during the inspiratory phase, $n_1 > n_2$. Therefore, $P_1 > P_2$.

If the inspiratory phase has the same duration in both cases, then the slope of the inspiratory segment of the pressure curve during dry air breathing must exceed that during humid air breathing by a factor n_1/n_2. The slope of the expiratory segment of the pressure curve however in this case does not change (fig. 11b).

When several breaths of dry air are taken after breathing humid air, the following changes occur :

- the slope of the inspiratory segment in the fast component increases
- the slow component assumes an ascending course.

Let us now consider the other extreme, a constant-pressure body plethysmograph in open communication with the environment. In this case the time constant of the leak from the body plethysmograph to the environment approaches zero ($\tau_1 \rightarrow 0$). Again we use the equation PV = nRT. P is constant, therefore $V \sim nRT$.

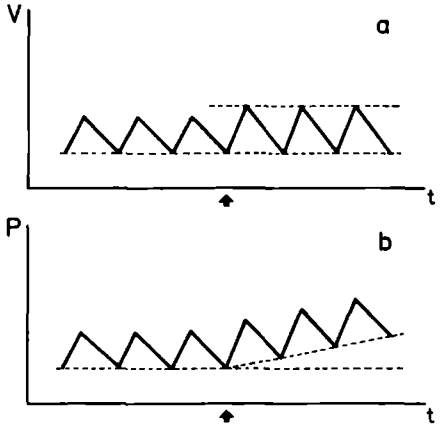

fig. 11. a. Constant-pressure body plethysmograph. Ordinate : volume (V), abscissa : time (s). After the change-over (arrow) from breathing humid air to dry air the fast component shows a steeper inspiratory and expiratory segment. The course of the slow component remains unchanged. b. Constant-volume body plethysmograph. Ordinate : pressure (P), abscissa : time (s). After the change-over (arrow) from breathing humid air to dry air the fast component shows a steeper inspiratory segment, the slope of the expiratory segment remains the same. The slow component of the curve shows an upward course after changing over.

During inhalation of dry air, n_1 H_2O molecules are added to the gas phase in the lungs; during inhalation of humid air this number is n_2. Again, $n_1 > n_2$. V_1 is the increase in volume during inhalation of dry air, and V_2 is the increase in volume during inhalation of humid air.

Assuming the temperature of the dry air to equal that of the humid air,

$$V_1 \sim n_1 \quad \text{and} \quad V_2 \sim n_2 \qquad \text{or} \qquad \frac{n_1}{n_2} = \frac{V_1}{V_2} .$$

Given a constant pressure in the body plethysmograph the slope of the inspiratory segment of the volume curve during inhalation of dry air exceeds

that during inhalation of humid air by a factor n_1/n_2. During the expiratory phase the pressure in the body plethysmograph can be kept equal to that in the environment by an inflow of n_1/n_2 times as much air into the body plethysmograph as during the expiratory phase of humid air breathing. Consequently the slope of the expiratory segment of the curve exceeds that during humid air breathing by a factor n_1/n_2. The reversal point to the next inspiratory segment, therefore, remains on the same level as that in the preceding respiratory cycle. Thus the course of the slow component will not change (fig. 11a).

When a subject in the constant-pressure body plethysmograph takes several breaths of dry air after first breathing relatively humid air, the following changes occur :

- the slope of the inspiratory segment (rapid component) of the volume curve increases
- the slope of the expiratory segment (rapid component) of the volume curve increases.

Our body plethysmograph has a time constant of about 60 s. Therefore the course of the curve when the change is made from humid air breathing to dry air breathing lies between the two extremes shown in fig. 11a and 11b. In order to avoid this problem in the determination of PCB, dry air breathing will be compared with the breathing of a dry $N_2O + O_2$ mixture. If a possible occurring difference in humidity between air and $N_2O + O_2$ mixture is disregarded, substantial errors may be incurred in the determination of PCB

4.3.2.4. The literature concerning inspiratory water vapour pressure

In the available literature we have found no data on all these phenomena and the problems related to them. Regarding water vapour pressure of the air used as a reference gas and that of the $N_2O + O_2$ mixture, the following divergent methods are being used in registration of PCB.

a. The subject first breathes air from the body plethysmograph and then a $N_2O + O_2$ mixture from a balloon inside the body plethysmograph

b. (LEE & DUBOIS 1955; LINDERHOLM et al. 1962; BOSMAN et al. 1964). The subject first breathes air from the room in which the body plethysmograph is placed and then a $N_2O + O_2$ mixture from a balloon outside the body plethysmograph (VERMEIRE & BUTLER 1968).

c. The subject re-breathes, first from a balloon filled with heated humid air and then from one filed with heated humid $N_2O + O_2$ mixture at BTPS conditions (DUBOIS & MARSHALL 1957).

ad a. The publications of LEE & DUBOIS and LINDERHOLM et al. have discussed the determination of PCB by the apnoea method in a constant volume body plethysmograph. In determining PCB the difference in water vapour pressure between the air from the body plethysmograph and the $N_2O + O_2$ mixture from the balloon was not taken into account. Our experiment has shown that breathing a dry gas mixture after breathing humid air from the body plethysmograph causes an increase in differential pressure between the body plethysmograph and the environment. The curve obtained during the apnoea period after inhalation of the dry gas mixture consequently takes a steeper course. In this context the method used by BOSMAN et al. is also subject to criticism. BOSMAN et al. had a subject inhale to maximum depth and determined PCB during the subsequent slow exhalation. He used a body plethysmograph equipped with a servo-mechanism by which the pressure in the body plethysmograph was kept equal to that prevailing in the environment. In principle, his body plethysmograph can be compared with a constant-pressure body plethysmograph. At a difference in inspiratory water vapour pressure of only 5 mm Hg between breathing air and breathing a $N_2O + O_2$ mixture, the error in the calculation of PCB is already 7% (given a PCB of 6 l/min and an alveolar N_2O fraction of 40%).

ad b. Since in the method used by VERMEIRE & BUTLER, too, the water vapour pressure of the air and that of the $N_2O + O_2$ mixture were not the same, their procedure has the same inherent defect as that described by BOSMAN.

ad c. DUBOIS & MARSHALL determined PCB in a constant-volume body plethysmograph. Temperature and water vapour pressure of the air serving as reference gas were the same, and the above mentioned source of error was therefore avoided.

Conclusion :
The difference in inspiratory water vapour pressure between the air used as reference gas and the $N_2O + O_2$ mixture gives rise to errors in the determination of PCB. This applies both to determinations made in the constant-volume as well as those made in the constant-pressure body plethysmograph. Reports so far published have failed to take this into consideration.

4.3.3. Temperature of the inspiratory gas

It is theoretically possible that the air in the body plethysmograph has a higher temperature than the air or gas mixture in the balloon inside the body plethysmograph. The subject heats the air in the body plethysmograph. The plastic wall of the balloon provides a certain insulation. The rise in temperature in the body plethysmograph therefore does not immediately cause an equal rise in temperature of the air or gas mixture in the balloon. Moreover, the dry air or gas mixture is drawn from a cylinder in which a high pressure prevails. The adiabatic expansion which occurs when the gas escapes from the cylinder causes a decrease in the temperature of the gas. The specific heat of gases, however, is low. Heat is also gained via the tubing through which the gas flows from the cylinder to the balloon inside the body plethysmograph.

This is the reason why we compared the temperature of the air in the body plethysmograph with that of the dry gas in the balloon immediately after filling. Temperature was registered by means of thermistors suitable for this purpose. No difference in temperature was registered. A subject entering the body plethysmograph did not alter this fact. Correction of the pneumotachograph signal for changes in temperature of the inspired gas was therefore unnecessary.

4.3.4. Rate of expiration

In the procedure described by VERMEIRE & BUTLER (1968) and that described by BOSMAN et al. (1964), PCB was determined during slow expiration. We wanted to know therefore the relationship that exists between the rate of expiration and the slope of the descending segment

of the rapid component of the pressure curve. For this purpose a subject entered the body plethysmograph and, with the aid of the one-way valve, breathed a constant inspiratory volume. After 3 min the subject increased his rate of expiration during ten consecutive respiratory cycles, and then returned to a lower rate of expiration. Meanwhile we registered the differential pressure between the body plethysmograph and the inside reference vessel, inspiratory volume and inspiratory and expiratory pneumotachogram.

Of the curves registered, the slope of the descending (expiratory) segment was plotted against expiratory flow. An example is shown in fig. 12.

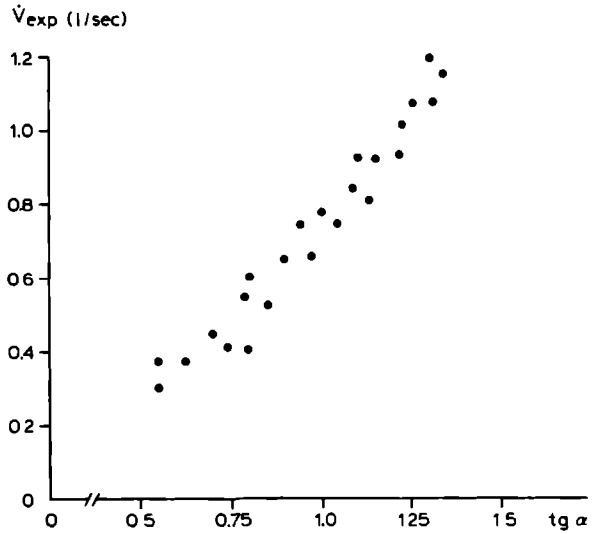

fig. 12. Relation between expiratory flow ($\dot{V}_{exp}$) and the slope (tgα) of the expiratory segment. Note the scatter of the values.

The curve thus obtained suggests curvi linearity but the scatter is large. DUBOIS & MARSHALL who determined PCB during in- and expiration corrected the pressure signal of the body plethysmograph by means of the pneumotachograph signal. But such a procedure would give rise to substantial errors in our body plethysmograph.

We attribute this scatter mainly to the variable breathing pattern during the procedure. This is the reason, why energy release by the subject

differs in the consecutive respiratory cycles, causing deflections in the course of the slow component of the pressure curve, which in turn will cause deviation from the ideal course as shown in fig. 9.

4.4. Determination of pulmonary capillary bloodflow and the physical properties of the constant-volume body plethysmograph

4.4.1. Introduction

In chapter 3 the complex physical properties of the body plethysmograph have already been discussed. In view of this it is evident that a subject performing a respiratory manoeuvre may induce a number of variations in the determination. Working with the constant-volume body plethysmograph and using the existing procedures established by LEE & DUBOIS (1955) and BOSMAN et al. (1964), we obtained PCB values of poor reproducibility.

4.4.2. The apnoea method and the slow expiration method

Using the apnoea method LEE & DUBOIS proceeded as follows. After a deep expiration the subject inhaled to maximum depth. He then exhaled to FRC level and held his breath with open glottis. The respiratory manoeuvre was executed, first with air from the body plethysmograph, and after an interval (motivated by the authors as ensuring return to an identical initial situation) with an $N_2O + O_2$ mixture. Using this procedure, we found that the slope of the curve during the apnoea period after breathing air was determined by the following factors :

1. The time constant of the leak from the body plethysmograph to the environment and the actual differential pressure between the body plethysmograph and the environment;
2. The energy relations between the subject, the body plethysmograph and the environment. During a respiratory manoeuvre, the continuity of the energy release by the quietly breathing subject is interrupted. During fast inhalation to maximum depth, the energy released per unit of time into the body plethysmograph in the form of heat and water vapour is greater than before. Consequently and also as a result of the increased pressure gradient between the alveolar space and the body

plethysmograph, the differential pressure increases markedly. During expiration to FRC level the differential pressure decreases because the pressure gradient between the alveolar space and the body plethysmograph is reversed. The differential pressure decreases further during the breath-holding phase. This further decrease during this phase is due to the fact that energy release from the body plethysmograph to the environment exceeds energy release from subject to the body plethysmograph. This phenomenon is analogous to the situation which prevails when the lamp inside the body plethysmograph is switched off (cf. fig. 4). During the apnoea phase, no energy is released in the form of respiratory heat and water vapour.

If the slope of the curve which indicates the differential pressure between the body plethysmograph and the inside reference vessel is to be kept constant during two consecutive apnoea periods, five requirements must be met, viz. :

1. The inspiratory volume best be kept the same in both cases;
2. The differential pressure between the body plethysmograph and the environment at the start of the apnoea phase must be the same in both cases;
3. The slope of the slow component of the curve which indicates the course of differential pressure between the body plethysmograph and the inside reference vessel must be the same in both cases;
4. In both cases the subject must exhale to the same lung volume;
5. Water vapour pressure and temperature of the inspiratory gas mixture must be the same in both cases.

When the BOSMAN procedure is carried out in the constant-volume body plethysmograph, an additional requirement must be met. In that case the rate of expiration during the respiratory manoeuvre must be the same in both cases.

We ascribe the poor reproducibility of PCB values obtained by these methods to the fact that a large number of factors have to remain constant. We therefore raised the question whether a method involving fewer variables would not be preferable for the determination of PCB.

Such a method would have to meet the following requirements :

1. The subject's energy release pattern should be constant and readily reproducible;
2. The respiratory manoeuvre should be as simple as possible.

In our opinion it is logical to determine PCB in a quietly breathing subject. In that case the disturbance of the energy relations is minimized, and execution of complex respiratory manoeuvres is superfluous.
A point that needs clarification now is the distribution of the ventilation-perfusion ratios in the lungs; during multiple breath, wash-in measurements. BRYAN et al. (1964) compared the distribution of the ventilation in a single breath measurement with that during a wash-in multiple-breath measurement. In normal subjects they found identical results with both methods. MILIC-EMILI et al. (1966) observed that the proportion of inspired gas delivered into various lung regions is constant when varying the total lung capacity between 20 and 100%. One should bear in mind that it is unlikely that the uneveness of the distribution of the ventilation-perfusion ratios, which occurs during normal breathing, affects the validity of the measurement of PCB. Since the absorption of N_2O in each region of the lung is proportional to the concentration of N_2O in that region, and only the N_2O-concentration of mixed alveolar gas is considered in the calculation of the blood flow, no appreciable error will be introduced as long as all regions of the lungs receive at least some N_2O, during each inspiration i.e. no intrapulmonary shunt nor alveolar dead space prevails.

CHAPTER 5. THE MULTIPLE-BREATH METHOD TO DETERMINE PULMONARY CAPILLARY BLOOD FLOW

5.1. Introduction

The principle on which our method is based consists in determining PCB by a multiple breath procedure during wash-in of a N_2O containing gas mixture.

5.2. Description of this method

In this new method it is essential to keep the subject's inspiratory volume constant. This necessity has already been discussed. To ensure this we used the pneumotachograph-controlled shutter and the one-way valve which could be adjusted to any desired volume between 300 and 2000 ml. The intervals between the inspiratory movements and the depth to which the subject exhaled had to remain as constant as possible. This posed no problems with the majority of subjects and patients. Determination should not be started until at least 3.5 min after the subject enters the body plethysmograph (3.2.1. and fig. 9). The ventilating valve must not be used (3.2.5. and fig. 10). The breathing of the dry $N_2O + O_2$ mixture must be preceded by a period of breathing dry air (4.3.2. and fig. 10). Unless these requirements are met, changes which occur in the slope of the slow component may interfere with the change in the slope which occurs during breathing of the $N_2O + O_2$ mixture.

5.2.1. Procedure

The subject entered the body plethysmograph, which was then closed. The subject then took the mouthpiece in his mouth, placed the clamp on his nose and breathed the pre-set inspiratory volume (pre-set so as to ensure that the subject had no subjective discomfort when breathing). The inspiratory volume was usually 1.5 - 2 times the tidal volume customary for the subject involved. After 3.5 min we checked whether the differential pressure between the body plethysmograph and the inside reference vessel was within the range of the differential manometer. This

was usually the case after 3.5 - 5 min. Once the slow component of the curve started to take a linear course the subject (or patient) was switched from breathing air from the body plethysmograph to breathing dry air from the balloon inside the body plethysmograph. We paused until the curve assumed a stable, predictable course (usually after about ten inhalations of dry air) and then switched the subject to a second balloon, containing a dry $N_2O + O_2$ mixture. This mixture was inhaled during 20 - 30 s, the inspiratory pneumotachograph being adjusted to ensure that the inspiratory volume remained the same as when the subject was breathing air. In this procedure the following variables were registered :

1. Differential pressure between the body plethysmograph and the inside reference vessel;
2. N_2O fraction (measured as NO-fraction, mass number 30), O_2 fraction and H_2O fraction of the respiratory gas;
3. Inspiratory volume;
4. Inspiratory pneumotachogram;
5. Expiratory pneumotachogram.

PCB was determined in 20 resting subjects aged 24 - 46. In the determinations of resting PCB the subjects were seated on a chair for 5 min before entering the body plethysmograph. A helium wash-out curve and CO_2 curve according to GREVE (1960) were known for all subjects. Since all these curves were found to be within normal limits, it was assumed that the distribution of the ventilation-perfusion ratios in the lungs was normal. In 6 subjects the determination was performed twice.

In 8 subjects PCB was determined during light exercise. This exercise consisted in the extension of a coil-spring to a length which corresponded to an expanding force of 6 kg. Resting PCB was determined 15 min before or after the exercise.

PCB was also determined in 7 resting patients with cardiovascular disorders. In this group helium wash-out and CO_2 curves also were within normal limits. In 5 of these patients PCB was determined 1 - 2 days before operation and 10 - 14 days after operation (four operations to replace one or two heart valves by prostheses; one operation for

coarctation of the aorta).

5.2.2. Calculation of PCB[x]

The following factors were used for the calculation of PCB.

1. The inspiratory N_2O fraction ($F_{I_{N_2O}}$).
2. The mean alveolar N_2O fraction during inspiration and expiration of the consecutive respiratory cycles ($F_{\bar{A}_{N_2O}}$) which was graphically determined from the N_2O wash-in curve as indicated by RIGATTO (1968).
3. The N_2O uptake during wash-in { $V_{m_{N_2O}}(t)$ } as measured by the body plethysmograph.
4. The duration of consecutive respiratory cycles.
5. The time constant of the leak from the body plethysmograph to the environment (τ_1).

The calculation was based on the following assumptions.

1. The volume change derived from the pressure change in the body plethysmograph is due solely to the uptake of N_2O by the blood perfusing the lungs.
2. At time t = 0, $F_{A_{N_2O}} = 0$.
3. $F_{I_{N_2O}}$ is constant.
4. The alveolar volume (V_A) is constant.
5. Ventilation ($\dot{V}$) is continuous.
6. PCB is constant ($\dot{Q}$) over several respiratory cycles.
7. The solubility of N_2O (S_{N_2O}) remains unchanged.
8. The product of $\dot{Q}$ and S_{N_2O} (k) is therefore also constant.
9. No recirculation occurs.

The equation which applies to wash-in of a gas which does not dissolve in the blood perfusing the lungs is :

x *The calculations were made possible by the invaluable help supplied by the Department of Medical Physics, Catholic University Nijmegen.*

$$F_A(t) = F_I \left(1 - e^{-t/\tau} \right) \quad (1)$$

in which $F_A(t)$ = alveolar gas fraction at time = t, F_I = inspiratory gas fraction and $\tau = \frac{V_A}{\dot{V}}$.

The equation which applies to wash-in of a gas which dissolves in the blood perfusing the lungs, such as N_2O, is :

$$F_{A_{N_2O}}(t) = F_{max_{N_2O}} \left(1 - e^{-t/\tau_{N_2O}} \right) \quad (2)$$

in which :

$$\tau_{N_2O} = \frac{V_A}{\dot{V}+k} \quad \text{and} \quad F_{max_{N_2O}} = \frac{\dot{V}}{\dot{V}+k} F_{I_{N_2O}}.$$

The amount of N_2O taken up per unit of time ($\dot{V}_{N_2O}$) by the blood perfusing the lungs is :

$$\dot{V}_{N_2O} = k.F_{A_{N_2O}}(t) = k.F_{max_{N_2O}} \left(1 - e^{-t/\tau_{N_2O}} \right) \quad (3)$$

$$= \dot{V}_{max_{N_2O}} \left(1 - e^{-t/\tau_{N_2O}} \right) \quad (4)$$

The amount of N_2O { $V_{N_2O}(t)$ } taken up after a time (t) is :

$$V_{N_2O}(t) = \int_0^t k.F_{A_{N_2O}}(t)\, dt \quad (5)$$

From equations (2) and (5) we obtain :

$$V_{N_2O}(t) = \tau_{N_2O} \cdot k.F_{max_{N_2O}} \{ t/\tau_{N_2O} - (1 - e^{-t/\tau_{N_2O}}) \} \quad (6)$$

$$\tau_{N_2O}.k.F_{max} = C \quad (7)$$

$$V_{N_2O}(t) = C\{ \quad ^{t/\tau_{N_2O}} - (1-e^{-t/\tau_{N_2O}}) \} \qquad (8)$$

In a test subject seated in the constant-volume body plethysmograph, the measured volume of N_2O $\{ V_{m_{N_2O}}(t)\}$ which during wash-in dissolves in the blood perfusing the lungs differs from the volume of N_2O actually dissolved $\{ V_{N_2O}(t)\}$. This difference is caused by the leak from the body plethysmograph to the environment (τ_1).

The relation between the $V_{m_{N_2O}}(t)$ and the above-mentioned factors is expressed by the equation :

$$V_{m_{N_2O}}(t) = C\{ \frac{\tau_1}{\tau_1 - \tau_{N_2O}} (e^{-t/\tau_{N_2O}} - e^{-t/\tau_1}) + \frac{\tau_1}{\tau_{N_2O}} (1-e^{-t/\tau_1}) \} \qquad (9)$$

C could be deduced by curve fitting of the N_2O wash-in curve and the N_2O uptake curve. In addition τ_{N_2O} was determined from the N_2O wash-in curve.

From equation (7) and assumption (8) we obtain :

$$\dot{Q} = \frac{C}{S_{N_2O} \cdot F_{max_{N_2O}}} \cdot \tau_{N_2O}$$

As may be deduced from equation (9) the measured amount of N_2O taken up $\{ V_{m_{N_2O}}(t) \}$ becomes smaller when the ratio τ_1/τ_{N_2O} lessens.

Consequently the measurement of PCB becomes less accurate when the time constant of the leak of the body plethysmograph with the environment shortens. However, when τ_1 is great, the subject has to remain in the body plethysmograph a long time before the determination can be started. In that case one has to wait till the pressure in the body plethysmograph, which rises to a high value, returns to a value within the measuring range of the differential manometer. Our body plethysmograph having a time constant of about 60 s allows a sufficiently accurate determination, while on the other hand the interval need not be too long before the

pressure is within the range of the manometer.

An example of a determination is shown in fig. 13 and 14.

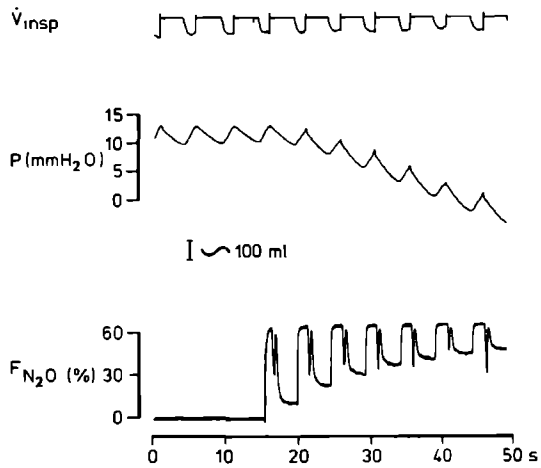

fig. 13. Example of a determination of PCB during N_2O wash-in. From top to bottom : Inspiratory pneumotachogram ($\dot{V}_{insp}$), differential pressure between the body plethysmograph and the inside reference vessel (P), N_2O fraction of the respiratory gas (F_{N_2O}).

The following comments can be made with regard to the above-metioned assumptions.

ad 4. When the volume of N_2O is measured with the aid of the body plethysmograph the alveolar volume plays no role because it was ensured that the changes in alveolar volume during $N_2O + O_2$ breathing were the same as those during air breathing. Since the curve obtained during air breathing is subtracted from the curve obtained during $N_2O + O_2$ breathing, only the pressure change of the N_2O uptake remains.

The equation used for the calculation of N_2O uptake by curve fitting presumes that the alveolar volume remains constant. Studies on the determination of the diffusion capacity by the multiple-breath CO method have shown that this assumption does not introduce any significant error in the calculation of the diffusing capacity (FORSTER et al. 1954). By

analogy we believe that in the multiple-breath N_2O method, too this assumption introduces no significant error. To what extent the use of an 'on line' computer bypasses this difficulty, still needs further investigation.

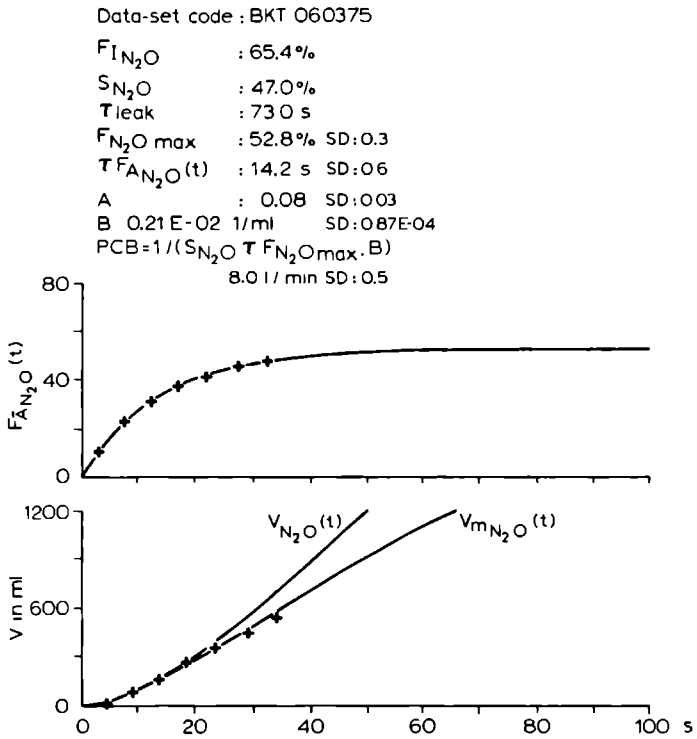

fig. 14. Computer print out of the same determination shown on fig. 13. Curve fitting makes possible to determine the correct value of N_2O uptake.

Upper curve. Ordinate : Mean alveolar N_2O-fraction ($\bar{F}_{A_{N_2O}}$) during consecutive respiratory cycles.

Abscissa : time (s).

Lower curve. Ordinate : Volume of N_2O taken up.

Abscissa : time (s).

For further explanation see text.

ad 5. As the volume of N_2O taken up is directly measured by means of the body plethysmograph, so also the alveolar N_2O fraction is directly measured by means of the mass spectrometer. The influence exerted on the alveolar air fraction by the fluctuations in alveolar volume during respiration is thus already accounted for. Otherwise the considerations mentioned ad 4 apply.
ad 6. It follows from this assumption that PCB calculated is a mean of PCB values during the wash-in of N_2O.
ad 9. As may deduced from the scanty literature on this subject, the volume of N_2O which recirculates during 30 s after breathing a gas mixture containing N_2O is small. An evident advantage of the multiple-breath method over the single-breath method in this context is the increase of the alveolar N_2O fraction during wash-in. At recirculation of N_2O the volume of N_2O which recirculates is related to the smaller alveolar N_2O fraction which prevailed in the lungs one circulation time earlier. With the single-breath method we have a decreasing alveolar N_2O fraction. The relative error due to recirculation incurred in this case exceeds the error in the multiple-breath method.

5.2.3. Calibration

The body plethysmograph was calibrated by registration of the pressure signal resulting from pumping 100 ml air into and out of the body plethysmograph. Pumping was done manually at a frequency of 0.2 Hz. Since N_2O uptake is a rapid process, the equation $PV^{1.2} = C$ (CIELEN 1971) applies. The influence of the time constant of the leak from the body plethysmograph to the environment on calibration was corrected by curve fitting, as already mentioned. The mass spectrometer was calibrated for N_2O with the aid of a test gas containing 39.8% N_2O and 60.2% air.

5.3. Results

5.3.1. PCB in resting subjects

Data on the subjects' age, sex, height, weight, body surface, PCB and PCB/m^2 body surface area (PCB/m^2) are presented in table 2.

TABLE 2 : PCB in resting subjects.

Subj. no.	Sex	Age (yr.)	Height (cm)	Weight (kg)	Body surf. (m^2)	Heart rate beats/ min	PCB l/min	PCB/m^2 l/min/ m^2	C.I.[x] pred. l/min/m^2	PCB/m^2 C.I. pred.
1	m	32	183	81	2.03	66	7.9	3.9	3.5	1.11
2	m	33	175	80	1.96	76	7.6	3.9	3.5	1.11
3	f	27	178	72	1.91	72	5.7	3.0	3.6	0.83
4	m	28	181	71	1.90	84	7.4	3.9	3.6	1.08
5	m	26	170	65	1.75	60	5.9	3.4	3.6	0.94
6	f	24	164	55	1.59	80	5.0	3.1	3.7	0.84
7	m	24	177	71	1.87	96	7.3	3.9	3.7	1.05
8	m	30	178	70	1.87	108	7.2	3.9	3.6	1.08
9	m	29	180	69	1.87	76	7.4	4.0	3.6	1.11
10	m	31	172	65	1.77	84	5.8	3.3	3.5	0.94
11	m	27	185	86	2.10	72	8.9	4.2	3.6	1.17
12	m	35	178	73	1.90	80	6.9	3.6	3.5	1.03
13	f	29	172	67	1.79	88	6.0	3.3	3.6	0.92
14	m	46	186	85	2.10	94	7.6	3.8	3.2	1.19
15	f	34	173	70	1.83	76	5.8	3.2	3.5	0.91
16	m	24	165	67	1.74	92	6.3	3.6	3.7	0.97
17	m	27	173	84	1.98	74	7.5	3.8	3.6	1.06
18	m	30	180	79	1.99	96	6.8	3.4	3.6	0.94
19	m	29	168	56	1.63	64	5.7	3.5	3.6	0.97
20	f	26	163	62	1.67	80	6.3	3.8	3.6	1.06

x : Predicted Cardiac Index according to the formula of PRYS-ROBERTS.

The body surface was calculated by applying the equation of DUBOIS & DUBOIS : $S = H^{0.725} \times W^{0.425} \times 71.84 \times 10^{-4}$, in which S = surface in m^2, H = height in cm, W = weight in kg. The mean PCB/m^2 was 3.6 l/min/m^2 (SD $\pm$ 0.4).

From cardiac output data published in the literature, PPYS-POBERTS (1974) calculated an equation for the cardiac index (CI), which reads as follows : CI = 4.16 - 0.02 x age (in years). The final column of the table gives the ratio of the PCB/m^2 value found here, and the predicted cardiac index. The mean value of this ratio is :

$$\frac{\text{PCB/min/m}^2}{\text{CI}} = 1.02 \ (\text{SD} \pm 0.10)$$

5.3.1.1. Consecutive determinations of PCB in resting subjects

TABLE 3 : Consecutive determinations of PCB in resting subjects.

				1st determination			2nd determination			
Subj. no.	Sex	Age	Body surf.	Heart rate beats/ min	PCB l/min	PCB/m^2 l/min/ m^2	Heart rate beats/ min	PCB l/min	PCB/m^2 l/min/ m^2	d_i^x l/min/ m^2
1.	f	24	1.75	84	5.8	3.3	80	6.9	3.9	+ 0.6
2.	m	30	1.78	68	7.2	4.0	72	6.8	3.8	- 0.2
3.	m	46	2.10	64	7.4	3.8	68	7.9	4.0	+ 0.2
4.	f	34	1.73	92	6.0	3.5	92	5.2	3.0	- 0.5
5.	m	27	1.99	76	6.7	3.4	72	7.6	3.8	+ 0.4
6.	m	32	2.03	80	7.8	3.8	84	7.0	3.5	- 0.3

x : difference of PCB/m^2 between two consecutive determinations.

Physical data of the subjects and the results of determinations of PCB are listed in table 3. In consecutive determinations both the mean PCB/m^2 of the first and the second series of determinations were 3.6 l/min/m^2. The mean difference between two determinations was smaller than 0.1 l/min/m^2 (SD $\pm$ 0.4). The standard error of a single observation (SE_x) expressed as a percentage of mean PCB/m_2 was 7.7%. SE_x was calculated according to the formula given by RÜMKE & VAN EEDEN (1961) :

$$SE_x = \sqrt{d_i^2 / 2n}$$

in which d_i = difference between two consecutive determinations
n = number of paired determinations.

5.3.2. PCB in subjects during light exercise

Physical data of the subjects and the results of determinations of resting PCB and during exercise are presented in table 4, and figure 15. In resting subjects mean PCB /m^2 was 3.6 l/min/m^2, (SD $\pm$ 0.5). During exercise mean PCB /m^2 was 4.7 l/min/m^2, (SD $\pm$ 0.6). The mean difference between exercise and resting values was 1.1 l/min/m^2 (SD $\pm$ 0.4).

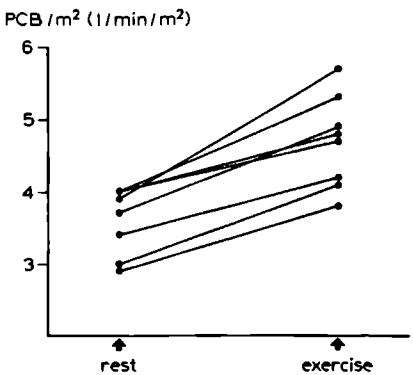

fig. 15. Diagram showing the effect of exercise on PCB.

TABLE 4 : Influence of exercise on PCB.

				rest			exercise			
Subj. no.	Sex	Age	Body surf. (m^2)	Heart rate beats/ min	PCB l/min	PCB/m^2 l/min/ m^2	Heart rate beats/ min	PCB l/min	PCB/m^2 l/min/ m^2	d_e x l/min/m2
1.	f	24	1.75	88	5.9	3.4	100	7.3	4.2	+ 0.8
2.	m	32	1.91	72	7.6	4.0	96	9.0	4.7	+ 0.7
3.	m	30	1.91	64	5.7	3.0	84	7.9	4.1	+ 1.1
4.	f	26	1.85	100	7.3	4.0	108	8.9	4.8	+ 0.8
5.	m	46	2.10	72	6.1	2.9	96	8.0	3.8	+ 0.9
6.	m	33	1.95	68	7.3	3.7	92	9.6	4.9	+ 1.2
7.	f	30	1.84	80	7.1	3.9	104	10.5	5.7	+ 1.8
8.	m	29	1.85	92	7.4	4.0	116	9.9	5.3	+ 1.3

x : difference between exercise and resting values of PCB/m^2.

5.3.3. PCB in patients with cardiovascular disorders

Physical data of these patients and results of determinations of PCB are presented in table 5. Before operation mean PCB/m^2 was 3.0 l/min/m^2, (SD $\pm$ 0.6). The ratio of PCB/m^2 and predicted cardiac index was 0.96, (SD $\pm$ 0.18).
After operation mean PCB/m^2 was 3.3 l/min/m^2, (SD $\pm$ 1.2). The ratio of PCB/m^2 and predicted cardiac index was 1.02, (SD $\pm$ 0.36).

The figures obtained in patient no. 1 show an interesting aspect. Before operation PCB/m^2 was a little lower as aspected (2.7 l/min/m^2 instead of 3.3 l/min/m^2). After operation (aortic valve replacement) he developed supra ventricular tachycardia and went into heart failure. He was treated with beta blocking drugs. Postoperative PCB/m^2 values, taken on the 10th and 12th day differed considerably from the preoperative value (1.7

TABLE 5 : PCB in patients with Cardiovascular Disorders.

Pat. no.	Sex	Age	Diagn.	Operation	Before operation: Heart rate beats/min	PCB l/min	PCB/m² l/min/m²	C.I.x pred. l/min/m²	After operation: Heart rate beats/min	PCB l/min	PCB/m² l/min/m²
1	m	45	A.S. A.I.	implantation aortic valve prosthesis	96	5.4	2.7	3.3	88 92 76	3.4 3.6 7.1xx	1.7 1.8 3.5xx
2	f	62	A.S. A.I.	implantation aortic valve prosthesis	88	3.6	2.4	2.9	92	4.0	2.6
3	m	45	C.A.	resection isthmus	60	6.8	3.5	3.3	56	6.2	3.2
4	f	38	T.I. M.I.	implantation tricuspedal and mitral valve prosthesis	76	5.4	3.4	3.4	88	6.4	4.0
5	f	61	M.I.	implantation mitral valve prosthesis	108	6.2	3.6	2.9	not performed		
6	f	48	A.S. A.I.	implantation aortic valve prosthesis	120	6.0	3.6	3.2	130	7.9	4.8
7	m	57	A.I. A.S.	not operated	84	4.0	2.1	3.0			

x : Predicted cardiac index according to the formula of PRYS-ROBERTS.
xx : PCB 6 months after operation.

A.I. = Aortic Incompetence.
A.S. = Aortic Stenosis.
C.A. = Coartatio Aortae.
T.I. = Tricuspedal Incompetence.
M.I. = Mitral Incompetence.

$l/min/m^2$ and 1.8 $l/min/m^2$ respectively).
When seen again six months later, he was in good health. He was still using only a low dose of beta blocking drugs. There were no signs of cardiac insufficiency. Now his PCB/m^2 was 3.5 $l/min/m^2$, which is entirely in the normal range.

All patients were able to carry out the respiratory procedure without difficulty. The breathing of a constant inspiratory volume, posed no problems. The slight dizziness which occurred after breathing the N_2O + O_2 mixture was not experienced as discomfort by any of the patients.

5.4. Discussion

The values we found for PCB/m^2 body surface area agree well with those in the literature (PRYS-ROBERTS) for cardiac index. In principle PCB is always lower than the cardiac output because the volume of blood which reaches the left heart via an anatomical or physiological shunt is not measured. The determination measures only the volume of blood which flows past ventilated alveoli. In healthy subjects the shunt percentage is about 3%. Taking this into account, we find that the mean value we obtained for PCB/m^2 is about 5% higher than those found for cardiac index in the literature. The studies including cardiac index values, however, involved mostly determinations of cardiac output in subjects in the supine position, usually with a catheter in the pulmonary artery or a great vein and in a peripheral artery. These individuals were probably closer to basal conditions because they were supine and had to remain in this position for a considerable time because of the catheterization procedure. Another plausible explanation of the slightly higher values found here for PCB/m^2 might be that we disregarded in our calculations the volume of N_2O dissolved in the pulmonary parenchyma. Using a small plethysmograph (25 l), LEE & DUBOIS (1955) and RIGATTO et al. (1961) attempted to measure the volume of N_2O dissolving in the pulmonary parenchyma of dogs. LEE & DUBOIS measured an uptake of N_2O by the lung parenchyma which proved to be no more than 1% of the N_2O uptake by the blood perfusing the lungs. RIGATTO et al. were unable to measure any N_2O uptake by lung parenchyma. CANDER & FORSTER (1950) and AYOTTE (1970) concluded that

this percentage is much larger and amounts to 5 - 8%. However, this was only an assumption, and not a value obtained by direct measurement. We have therefore accepted the results published by LEE & DUBOIS and by RIGATTO et al., and disregarded the volume of N_2O which dissolves in the lung parenchyma when calculating N_2O uptake.
GUYTON (1968) points out that in the regulation of cardiac output the heart, under normal resting conditions, plays 'a permissive role'; the main factor determining cardiac output being the venous return to the heart.
Since slight movements of the limbs or trunk in sitting subjects may already affect venous return to the heart, variation in cardiac output for consecutive measurements may be expected to be greater than in subjects in the supine position.
In sitting subjects we found a good reproducebility of consecutive measurements of PCB/m^2 the mean coefficient of variation being 7.7%. For subjects in sitting rest we found in the literature a mean coefficient of variation for consecutive measurements of 10.2% (SALTIN, 1964) and 13.3% (FERGUSON et al. 1968). For subjects in the supine position values are reported between 5.5% (WERKÖ et al. 1949) and 9.2% (DONALD et al. 1953).

Movements of a subject during exercise in the body plethysmograph give rise to fluctuations in the course of the pressure curve. Since this would preclude an accurate determination, we adopted exercise in the form of an isometric contraction.
This type of exercise causes no disturbance in the course of the pressure curve, and accurate measurement is therefore possible.

The values for PCB we found in patients with cardiovascular disorders seem to be somewhat higher than those reported in literature for cardiac output. This may be caused by a systemic difference between the direct Fick or the dye-dilution method for determination of PCB in patients having a low cardiac output (cf. 1.2.1.).
Another reason may be that we investigated sitting non basal patients. Literature on determination of cardiac output by the direct Fick method or the dye-dilution method mostly involve patients in the supine position under more basal conditions. Finally the patients we investigated were

all ambulant. This already implies that only reasonably fit patients are involved in our study providing a certain degree of selection by possibly excluding patients with a low cardiac output.
Generally spoken we did not find marked differences between pre operative and post operative values for PCB in resting patients.

The clinical value of a single determination of cardiac output or PCB is limited. Only when the figure found for cardiac output or PCB deviates greatly from the expected figurs can this have clinical implications. Quantitative determinations of PCB should be evaluated mainly in relation to other physiological parameters or to PCB measured at a different time or under different conditions. PCB can be considered, for example, in relation to O_2 consumption. This can give information concerning the difference in O_2 content of the arterial and mixed venous blood. PCB also can be considered in relation to a standardized degree of exercise. When O_2 consumption is measured simultaneously the influence of exercise on arterio-venous O_2 difference can be examined.

Although it is often difficult to derive conclusions concerning the clinical course from a single series of determinations, yet from the serial determination of PCB in patient no. 1 one might be able to follow the condition of this patient after aortic valve replacement.
The figure indicating PCB becomes also more meaningful when considered in relation to the qualitative features of PCB (section 1.2.2.). Serial determinations of quantitative and qualitative PCB can be particularly useful in patients with mitral valve anomalies since it may be possible to diagnose pulmonary hypertension.

In our opinion the main justification for measuring PCB lies in the safe and simple application of the method, e.g. in the follow-up of patients with cardiovascular disorders. Unlike the usual methods for measuring cardiac output the determination of PCB is non-invasive. Invasive methods demand the use of indwelling catheters, thereby increasing the hazards with which these patients are faced.
Up till now it is impossible to determine the qualitative features of PCB by the multiple breath method.

The pressure changes in the body plethysmograph due to the pulsatility of the N_2O uptake are in the range of only 0.05 - 0.2 mm H_2O. The pressure changes due to the changing respiratory flow during normal breathing invalidate any registration of pulsatile N_2O-uptake. Consequently we think that for the determination of qualitative PCB the apnoea or the slow expiration method are mandatory. For the quantitative determination we prefer the multiple breath method which appears - due to its simple breathing manoeuvre and minimal disturbance in the energy relations between the subject, the body plethysmograph and the environment - to be a reliable measurement.

SUMMARY

Determination of pulmonary capillary blood flow (PCB) in the body plethysmograph is based on the measurement of the volume of N_2O which dissolves in the blood perfusing the lungs per unit of time. If the alveolar N_2O fraction is simultaneously determined, then PCB can be calculated with the aid of the BORNSTEIN equation. Up to now it has been customary to determine PCB during apnoea or slow expiration.

Following the procedures described and using the constant-volume body plethysmograph, we obtained poorly reproducible PCB values. Initially we attributed this to the difficulty which many subjects encounter in performing the breathing procedure correctly. We soon found, however, that reliable determination of PCB is impossible without a full understanding of the physical properties of the body plethysmograph.

Our study thus had a dual purpose : to evolve a less difficult breathing procedure, and to investigate pertinent physical properties of the body plethysmograph. The literature on the determination of PCB underestimates the importance of a knowledge of the physical properties of the body plethysmograph.

Since a test subject in the body plethysmograph releases heat as well as water vapour, we studied the course of the pressure curve in the body plethysmograph during consecutive and simultaneous production of heat and water vapour. When only heat was produced, the curve which indicates the differential pressure between the body plethysmograph and the outside reference vessel proved to take a characteristic course. This curve attained a maximum 100 s after starting the heat production (by switching on a lamp). The time at which the maximum was attained was constant, regardless of the size of the heat source. The value of the maximum was influenced by the size of the heat source. It was found impossible to increase the water vapour pressure in the body plethysmograph quickly without thermic disturbance. The effect of an increase in water vapour pressure was therefore simulated by insufflating air into the body plethysmograph. The pressure curve then registered in the body plethysmo-

graph of an exponential course. Simultaneous insufflation of air and activation of the heat source produced a pressure curve which approached that obtained after a subject entered the body plethysmograph. This pressure course revealed significant changes in the slope of the curve. If these changes are disregarded, errors will emerge when determining PCB.

Use of the ventilating valves in the body plethysmograph also caused marked changes in the slope of the pressure curve. The relay which controls the ventilating valve in the inside reference vessel can also exert a disturbing influence. All these factors therefore can be sources of error in determining PCB.

We have also established that the differential pressure between the body plethysmograph and the inside reference vessel was lower than between the body plethysmograph and the outside reference vessel. This was caused by an increase in pressure in the inside reference vessel resulting from heating of the reference vessel by the heat source or a subject in the body plethysmograph. When working with subjects, registration of the differential pressure between the body plethysmograph and the inside reference vessel had the advantage that determination could start earlier.

Next we discussed the factors which determine the pressure course in the body plethysmograph with a subject inside. Special attention was paid to the influence of the inspiratory volume, the inspiratory water vapour pressure and the expiratory flow. It was found from these studies that significant errors in the determination of PCB may be incurred when the inspiratory water vapour pressure of the reference air and that of the $N_2O + O_2$ mixture are not identical. The literature available to us makes no mention of this source of error. In the majority of reports the difference in water vapour pressure between reference air and $N_2O + O_2$ mixture is disregarded.

A curvi linear correlation seemed to exist between expiratory flow and slope of the expiratory segment of the pressure curve. However, the scatter of the values obtained was large. An attempt to correct the

pressure signal with the aid of the expiratory flow therefore did not seem justified.

In the determination of PCB, whether by the apnoea or by the slow expiration method, a great many variables have to be identical during air breathing and $N_2O + O_2$ breathing. In order to meet these requirements more readily, we adopted a multiple-breath method which also made it possible to simplify the breathing procedure. With the aid of a specially designed valve the inspiratory volume was kept constant during air breathing as well as during $N_2O + O_2$ wash-in. The N_2O fraction of the respiratory air was registered with the aid of a mass spectrometer.

PCB was determined in 20 resting subjects. The values correlated well with data obtained from the literature. In 8 subjects resting PCB was compared with PCB during light exercise. As aspected in all cases a higher PCB was measured during exercise.

Finally PCB was determined in 7 patients with cardiovascular disorders. In 5 of these patients the determination was made before and after an operation (in 4 cases performed to replace a heart valve).

Subjects as well as patients were able to carry out the breathing procedure without difficulty. None was really inconvenienced by the slight dizziness which occurred after breathing the $N_2O + O_2$ mixture.

De bepaling van de pulmonale capillaire bloedstroom (PCB) in de lichaamsplethysmograaf berust op het meten van de hoeveelheid N_2O, die per tijdseenheid oplost in het door de longen stromende bloed. Bij gelijktijdige bepaling van de alveolaire N_2O-fractie kan met behulp van de formule vlg. BORNSTEIN de PCB worden berekend. Tot nu toe was het gebruikelijk de PCB te bepalen tijdens apnoe of langzame expiratie.
Bij de bepaling van de PCB met de bovengenoemde ademprocedures kregen wij - werkend met de volumeconstante lichaamsplethysmograaf - slecht reproduceerbare waarden voor de PCB.
Wij schreven dit aanvankelijk grotendeels toe aan het feit, dat de ademprocedure voor veel proefpersonen moeilijk uitvoerbaar is.
Al spoedig bleek ons echter, dat een betrouwbare meting van de PCB onmogelijk is, als men niet geheel op de hoogte is van de fysische eigenschappen van de gebruikte lichaamsplethysmograaf.
Ons doel was daarom tweeledig; enerzijds het ontwikkelen van een eenvoudiger ademprocedure, anderzijds het onderzoeken van de in dit verband belangrijke fysische eigenschappen van de lichaamsplethysmograaf. In de literatuur over de bepaling van de PCB wordt namelijk voorbijgegaan aan het belang der kennis van de fysische eigenschappen van de lichaamsplethysmograaf. Omdat een proefpersoon in de lichaamsplethysmograaf zowel warmte als waterdamp afgeeft, gingen wij na hoe het drukverloop in de lichaamsplethysmograaf was, wanneer hier achtereenvolgens - en gelijktijdig - warmte en waterdamp aan werd toegevoegd. Bij toevoeging van alleen warmte bleek de curve, die het verloop weergeeft tussen lichaamsplethysmograaf en het hier buiten beplaatste referentievat, een typisch karakter te hebben. 100 s na het aanzetten van de warmtebron gaf deze curve een maximum te zien. Het tijdstip, waarop dit maximum optrad was steeds hetzelfde en onafhankelijk van de grootte van de warmtebron. De hoogte van het maximum werd wel beïnvloed door de grootte van de warmtebron. Het snel verhogen van de waterdampspanning in de lichaamsplethysmograaf bleek niet mogelijk zonder thermische verstoring. Daarom werd het effect van de verhoging van de waterdampspanning gesimuleerd door het inblazen van lucht in de lichaamsplethysmograaf. De drukcurve, die dan in de lichaamsplethysmograaf werd geregistreerd had bij benadering een exponentieel

verloop. Wanneer gelijktijdig met het aanzetten van een warmtebron lucht in de lichaamsplethysmograaf werd geblazen had de resulterende drukcurve een grote gelijkenis met die nadat een proefpersoon had plaats genomen in de lichaamsplethysmograaf. Bij beschouwing van deze drukcurve bleken hier aanzienlijke hellingsveranderingen in voor te komen. Veronachtzaming van deze veranderingen kan fouten veroorzaken bij de bepaling van de PCB.
Het bleek dat het gebruik van de in de lichaamsplethysmograaf aanwezige ventilatiekleppen eveneens aanleiding gaf tot grote hellingsveranderingen in de drukcurve. Ook ging er een storende invloed uit van het relais, dat de ventilatieklep in de het binnen lichaamsplethysmograaf geplaatste referentievat bedient. Factoren, die eveneens fouten in de bepaling van de PCB kunnen veroorzaken.
Bij de bovengenoemde proefopstellingen stelden wij bovendien vast, dat de differentiaaldruk tussen lichaamsplethysmograaf en een hierbinnen geplaatst referentievat lager was dan de differentiaaldruk tussen lichaamsplethysmograaf en een hierbuiten geplaatst referentievat. Dit werd veroorzaakt door de drukstijging in het binnen de lichaamsplethysmograaf geplaatste referentievat. Deze drukstijging was een gevolg van het verwarmen van het referentievat door de warmtebron of een proefpersoon. Registratie van de differentiaaldruk tussen lichaamsplethysmograaf en het hierbinnen geplaatste referentievat had bij proefpersonen als voordeel, dat er eerder met de meting kon worden begonnen.
Vervolgens bespraken wij de factoren, die het drukverloop in de lichaamsplethysmograaf beïnalen, wanneer hier een proefpersoon in had plaatsgenomen. De invloed van de grootte van het inspiratoir ademvolume, de grootte van de inspiratoire waterdampspanning en de grootte van de expiratoire flow had speciaal onze aandacht. Uit onze onderzoekingen kwam naar voren, dat er aanzienlijke fouten in de bepaling van de PCB kunnen ontstaan, wanneer de inspiratoire waterdampspanning van de als referentie dienende lucht en het $N_2O + O_2$-mengsel, niet identiek zijn. In de door ons geraadpleegde literatuur werd nergens melding gemaakt van deze foutenbron. In de meeste gevallen werd geen acht geslagen op het verschil in waterdampspanning van de als referentie dienende lucht en $N_2O + O_2$-mengsel.
Tussen de expiratoire flow en de helling van het met de expiratie samenhangende deel van de drukcurve leek een curvi-lineair verband te bestaan.

De spreiding van de gevonden waarden was echter groot. Een eventuele correctie van het druksignaal met behulp van de expiratoire flow leek ons daarom niet verantwoord.
Bij de bepaling van de PCB moeten - zowel bij de apnoe-methode als bij de langzaam expiratie-methode - een groot aantal variabelen identiek zijn tijdens het lucht ademen en het ademen van het $N_2O + O_2$-mengsel. Om aan deze eis gemakkelijker te kunnen voldoen werd gekozen voor een multiple breath-methode, waarbij bovendien de ademprocedure zeer eenvoudig is. Door gebruikmaking van een speciaal geconstrueerde klep werd het inspiratoire volume - zowel tijdens het ademen van lucht als tijdens de inwas van het $N_2O + O_2$-mengsel - constant gehouden. De N_2O-fractie van de ademhalingslucht werd geregistreerd met behulp van een massaspectograaf.

De PCB werd bepaald bij 20 proefpersonen in rust. De gevonden waarden bleken goed overeen te stemmen met die in de literatuur. Bij 8 proefpersonen werd de PCB in rust en tijdens lichte inspanning bepaald. In alle gevallen werd een hogere PCB gemeten tijdens inspanning.
Tenslotte werd bij 7 patiënten met cardiovasculaire aandoeningen de PCB bepaald. Bij 5 van deze patiënten werd de bepaling voor en na de operatie verricht. In 4 gevallen betrof het een operatie waarbij een hartklep werd vervangen.
Zowel de proefpersonen als de patiënten konden de gevolgde ademprocedure gemakkelijk volbrengen. De na de inademing van het $N_2O + O_2$-mengsel optredende lichte duizeligheid werd door geen van de personen als hinderlijk ervaren.

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De schrijver van dit proefschrift werd op 16 juli 1941 te Losser (Ov.) geboren. In 1959 legde hij het eindexamen H.B.S.-B af aan het St.Aloysius College te Den Haag. Vervolgens studeerde hij Geneeskunde aan de Rijksuniversiteit te Leiden. In december 1964 werd het doctoraalexamen afgelegd. Op 21 mei 1966 trouwde hij met Heleen van Brussel (op 4 maart 1970 werd hij vader van Cathelijne en op 28 december 1971 van Liselore). Op 28 april 1967 behaalde hij het artsexamen. Van juni 1967 tot september 1968 was hij verbonden aan de afdeling Interne Geneeskunde van het Centraal Militair Hospitaal te Den Haag (hoofden : A.D.A. van Overeem en Dr. M. van Zoeren). Van september tot december 1968 was hij werkzaam als waarnemend gouvernementsarts te Barber, Curacao. In december 1968 werd begonnen met de opleiding tot anesthesist aan het Instituut voor Anesthesiologie van het Sint Radboud Ziekenhuis te Nijmegen (directeur : Prof. Dr. J.F. Crul). In het kader van de opleiding anesthesiologie werd van december 1968 tot juni 1969 een stage algemene heelkunde gevolgd op de chirurgische afdeling van het St. Canisius Ziekenhuis (destijds hoofd van de opleiding : J.H.J.M. Pernet). Op 6 juni 1971 werd hij ingeschreven als anesthesist in het Specialistenregister van de Koninklijke Nederlandse Maatschappij tot Bevordering der Geneeskunst. Sinds 1 januari 1972 is hij als anesthesist verbonden aan het St. Canisius Ziekenhuis te Nijmegen.